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(54) **HETEROCYCLIC COMPOUNDS AND USES THEREOF**

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None

See application file for complete search history.

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(57) **ABSTRACT**

Compounds and pharmaceutical compositions that modulate kinase activity, including PI3 kinase activity, and compounds, pharmaceutical compositions, and methods of treatment of diseases and conditions associated with kinase activity, including PI3 kinase activity, are described herein.

24 Claims, No Drawings

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HETEROCYCLIC COMPOUNDS AND USES THEREOF

This application claims priority to U.S. Provisional Application Nos. 61/887,259, filed Oct. 4, 2013, 61/888,958, filed Oct. 9, 2013, and 61/938,026, filed Feb. 10, 2014, the entireties of which are incorporated herein by reference.

BACKGROUND

The activity of cells can be regulated by external signals that stimulate or inhibit intracellular events. The process by which stimulatory or inhibitory signals are transmitted into and within a cell to elicit an intracellular response is referred to as signal transduction. Over the past decades, cascades of signal transduction events have been elucidated and found to play a central role in a variety of biological responses. Defects in various components of signal transduction pathways have been found to account for a vast number of diseases, including numerous forms of cancer, inflammatory disorders, metabolic disorders, vascular and neuronal diseases (Gaestel et al. *Current Medicinal Chemistry* (2007) 14:2214-2234).

Kinases represent a class of important signaling molecules. Kinases can generally be classified into protein kinases and lipid kinases, and certain kinases exhibit dual specificities. Protein kinases are enzymes that phosphorylate other proteins and/or themselves (i.e., autophosphorylation). Protein kinases can be generally classified into three major groups based upon their substrate utilization: tyrosine kinases which predominantly phosphorylate substrates on tyrosine residues (e.g., erb2, PDGF receptor, EGF receptor, VEGF receptor, src, abl), serine/threonine kinases which predominantly phosphorylate substrates on serine and/or threonine residues (e.g., mTorC1, mTorC2, ATM, ATR, DNA-PK, Akt), and dual-specificity kinases which phosphorylate substrates on tyrosine, serine and/or threonine residues.

Lipid kinases are enzymes that catalyze the phosphorylation of lipids. These enzymes, and the resulting phosphorylated lipids and lipid-derived biologically active organic molecules play a role in many different physiological processes, including cell proliferation, migration, adhesion, and differentiation. Certain lipid kinases are membrane associated and they catalyze the phosphorylation of lipids contained in or associated with cell membranes. Examples of such enzymes include phosphoinositide(s) kinases (e.g., PI3-kinases, PI4-kinases), diacylglycerol kinases, and sphingosine kinases.

The phosphoinositide 3-kinases (PI3Ks) signaling pathway is one of the most highly mutated systems in human cancers. PI3K signaling is also a key factor in many other diseases in humans. PI3K signaling is involved in many disease states including allergic contact dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder, psoriasis, multiple sclerosis, asthma, disorders related to diabetic complications, and inflammatory complications of the cardiovascular system such as acute coronary syndrome.

PI3Ks are members of a unique and conserved family of intracellular lipid kinases that phosphorylate the 3'—OH group on phosphatidylinositols or phosphoinositides. The PI3K family comprises 15 kinases with distinct substrate specificities, expression patterns, and modes of regulation. The class I PI3Ks (p110α, p110β, p110δ, and p110γ) are typically activated by tyrosine kinases or G-protein coupled receptors to generate PIP3, which engages downstream effectors such as those in the Akt/PDK1 pathway, mTOR, the Tec family kinases, and the Rho family GTPases. The class II and III PI3Ks play a key role in intracellular trafficking through the synthesis of PI(3)P and PI(3,4)P2. The PI3Ks are protein kinases that control cell growth (mTORC1) or monitor genomic integrity (ATM, ATR, DNA-PK, and hSmg-1).

The delta (δ) isoform of class I PI3K has been implicated, in particular, in a number of diseases and biological processes. PI3K-δ is expressed primarily in hematopoietic cells including leukocytes such as T-cells, dendritic cells, neutrophils, mast cells, B-cells, and macrophages. PI3K-δ is integrally involved in mammalian immune system functions such as T-cell function, B-cell activation, mast cell activation, dendritic cell function, and neutrophil activity. Due to its integral role in immune system function, PI3K-δ is also involved in a number of diseases related to undesirable immune response such as allergic reactions, inflammatory diseases, inflammation mediated angiogenesis, rheumatoid arthritis, and autoimmune diseases such as lupus, asthma, emphysema and other respiratory diseases. Other class I PI3K involved in immune system function includes PI3K-γ, which plays a role in leukocyte signaling and has been implicated in inflammation, rheumatoid arthritis, and autoimmune diseases such as lupus. For example, PI3K-γ and PI3K-δ are highly expressed in leukocytes and have been associated with adaptive and innate immunity; thus, these PI3K isoforms can be important mediators in inflammatory disorders and hematologic malignancies.

The gamma (γ) isoform of class I PI3K consists of a catalytic subunit p110γ, which is associated with a p101 regulatory subunit. PI3K-γ is regulated by G protein-coupled receptors (GPCRs) via association with the β/γ subunits of heterotrimeric G proteins. PI3K-γ is expressed primarily in hematopoietic cells and cardiomyocytes and is involved in inflammation and mast cell function Inhibitors of PI3K-γ are useful for treating a variety of inflammatory diseases, allergies, and cardiovascular diseases, among others.

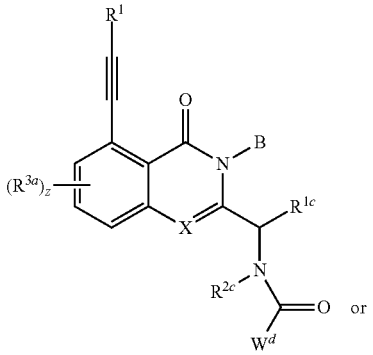
Unlike PI3K-δ, the beta (β) isoform of class I PI3K appears to be ubiquitously expressed. PI3K-β has been implicated primarily in various types of cancer including PTEN-negative cancer (Edgar et al. *Cancer Research* (2010) 70(3):1164-1172), and HER2-overexpressing cancer such as breast cancer and ovarian cancer.

SUMMARY

Described herein are compounds capable of selectively inhibiting one or more isoform(s) of class I PI3K without substantially affecting the activity of the remaining isoforms of the same class. For example, in some embodiments, non-limiting examples of inhibitors capable of selectively inhibiting PI3K-δ and/or PI3K-γ, but without substantially affecting the activity of PI3K-α and/or PI3K-β are disclosed. In one embodiment, the inhibitors provided herein can be effective in ameliorating disease conditions associated with PI3K-δ and/or PI3K-γ activity. In one embodiment, the compounds are capable of selectively inhibiting PI3K-γ over PI3K-δ.

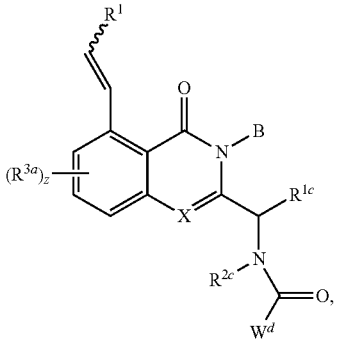
In one aspect, provided herein are compounds of Formula (I") or (A"):

Formula (I")



-continued

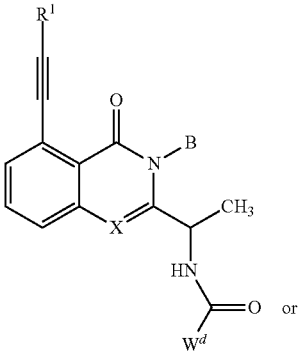
Formula (A″)



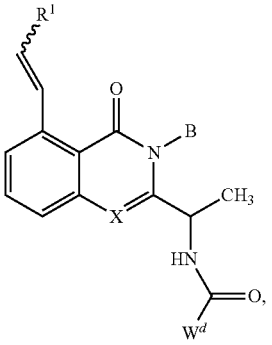
or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or a pharmaceutically acceptable form thereof, wherein R^{3a}, z, R^{1c}, R^{2c}, R^1, X, B, and W^d are defined herein.

In one aspect, provided herein are compounds of Formula (I') or (A'):

Formula (I')



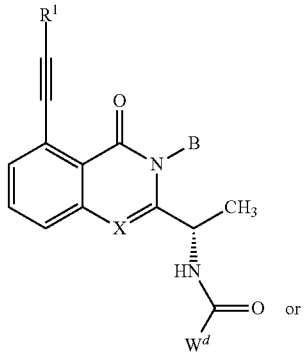
Formula (A')



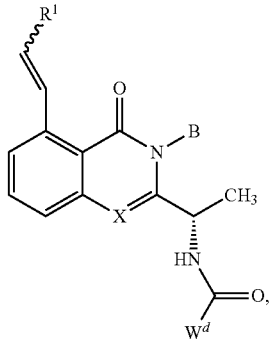
or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or a pharmaceutically acceptable form thereof, wherein R^1, X, B, and W^d are defined herein.

In one aspect, provided herein are compounds of Formula (I) or (A):

Formula (I)



Formula (A)



or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or a pharmaceutically acceptable form thereof, wherein R^1, X, B, and W^d are defined herein.

In one embodiment, the compound of Formula (I"), (I'), (I), (A"), (A'), or (A) is predominately in an (S)-stereochemical configuration. In one embodiment, the compound of Formula (I"), (I'), (I), (A"), (A'), or (A) is the S enantiomer having an enantiomeric excess selected from greater than about 25%, greater than about 55%, greater than about 80%, greater than about 90%, and greater than about 95%. In one embodiment, the compound is present in a pharmaceutical composition comprising the compound, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

In certain embodiments, a compound disclosed herein selectively modulates PI3K gamma isoform. In certain embodiments, the compound selectively inhibits the gamma isoform over the alpha or beta isoform. By way of non-limiting example, the ratio of selectivity can be greater than a factor of about 10, greater than a factor of about 50, greater than a factor of about 100, greater than a factor of about 200, greater than a factor of about 400, greater than a factor of about 600, greater than a factor of about 800, greater than a factor of about 1000, greater than a factor of about 1500, greater than a factor of about 2000, greater than a factor of about 5000, greater than a factor of about 10,000, or greater than a factor of about 20,000, where selectivity can be measured by ratio of IC_{50} values, among other means. In one embodiment, the selectivity of PI3K gamma isoform over PI3K alpha or beta isoform is measured by the ratio of the IC_{50} value against PI3K alpha or beta isoform to the IC_{50} value against PI3K gamma isoform.

In certain embodiments, a compound disclosed herein selectively modulates PI3K gamma isoform over the delta isoform. By way of non-limiting example, the ratio of selec-

tivity can be greater than a factor of about 10, greater than a factor of about 50, greater than a factor of about 100, greater than a factor of about 200, greater than a factor of about 400, greater than a factor of about 600, greater than a factor of about 800, greater than a factor of about 1000, greater than a factor of about 1500, greater than a factor of about 2000, greater than a factor of about 5000, greater than a factor of about 10,000, or greater than a factor of about 20,000, where selectivity can be measured by ratio of IC_{50} values, among other means. In one embodiment, the selectivity of PI3K gamma isoform over PI3K delta isoform is measured by the ratio of the IC_{50} value against PI3K delta isoform to the IC_{50} value against PI3K gamma isoform.

In certain embodiments, a compound as disclosed herein selectively modulates PI3K delta isoform. In certain embodiments, the compound selectively inhibits the delta isoform over the alpha or beta isoform. By way of non-limiting example, the ratio of selectivity can be greater than a factor of about 10, greater than a factor of about 50, greater than a factor of about 100, greater than a factor of about 200, greater than a factor of about 400, greater than a factor of about 600, greater than a factor of about 800, greater than a factor of about 1000, greater than a factor of about 1500, greater than a factor of about 2000, greater than a factor of about 5000, greater than a factor of about 10,000, or greater than a factor of about 20,000, where selectivity can be measured by ratio of IC_{50} values, among other means. In one embodiment, the selectivity of PI3K delta isoform over PI3K alpha or beta isoform is measured by the ratio of the IC_{50} value against PI3K alpha or beta isoform to the IC_{50} value against PI3K delta isoform.

In certain embodiments, provided herein is a composition (e.g., a pharmaceutical composition) comprising a compound described herein and a pharmaceutically acceptable excipient. In some embodiments, provided herein is a method of inhibiting a PI3 kinase, comprising contacting the PI3 kinase with an effective amount of a compound or a pharmaceutical composition described herein. In certain embodiments, a method is provided for inhibiting a PI3 kinase wherein said PI3 kinase is present in a cell. The inhibition can take place in a subject suffering from a disorder selected from cancer, bone disorder, inflammatory disease, immune disease, nervous system disease (e.g., a neuropsychiatric disorder), metabolic disease, respiratory disease, thrombosis, and cardiac disease, among others. In certain embodiments, a second therapeutic agent is administered to the subject.

In certain embodiments, a method is provided for selectively inhibiting a PI3 kinase gamma isoform over PI3 kinase alpha or beta isoform wherein the inhibition takes place in a cell. Non-limiting examples of the methods disclosed herein can comprise contacting PI3 kinase gamma isoform with an effective amount of a compound or a pharmaceutical composition disclosed herein. In an embodiment, such contact can occur in a cell.

In certain embodiments, a method is provided for selectively inhibiting a PI3 kinase gamma isoform over PI3 kinase alpha or beta isoform wherein the inhibition takes place in a subject suffering from a disorder selected from cancer, bone disorder, inflammatory disease, immune disease, nervous system disease (e.g., a neuropsychiatric disorder), metabolic disease, respiratory disease, thrombosis, and cardiac disease, said method comprising administering an effective amount of a compound or a pharmaceutical composition provided herein to said subject. In certain embodiments, provided herein is a method of treating a subject suffering from a disorder associated with PI3 kinase, said method comprising selectively modulating the PI3 kinase gamma isoform over PI3 kinase alpha or beta isoform by administering an amount of a compound or a pharmaceutical composition provided herein to said subject, wherein said amount is sufficient for selective modulation of PI3 kinase gamma isoform over PI3 kinase alpha or beta isoform.

In certain embodiments, a method is provided for selectively inhibiting a PI3 kinase delta isoform over PI3 kinase alpha or beta isoform wherein the inhibition takes place in a cell. Non-limiting examples of the methods disclosed herein can comprise contacting PI3 kinase delta isoform with an effective amount of a compound or a pharmaceutical composition disclosed herein. In an embodiment, such contact can occur in a cell.

In certain embodiments, a method is provided for selectively inhibiting a PI3 kinase delta isoform over PI3 kinase alpha or beta isoform wherein the inhibition takes place in a subject suffering from a disorder selected from cancer, bone disorder, inflammatory disease, immune disease, nervous system disease (e.g., a neuropsychiatric disorder), metabolic disease, respiratory disease, thrombosis, and cardiac disease, said method comprising administering an effective amount of a compound or a pharmaceutical composition provided herein to said subject. In certain embodiments, provided herein is a method of treating a subject suffering from a disorder associated with PI3 kinase, said method comprising selectively modulating the PI3 kinase delta isoform over PI3 kinase alpha or beta isoform by administering an amount of a compound or a pharmaceutical composition provided herein to said subject, wherein said amount is sufficient for selective modulation of PI3 kinase delta isoform over PI3 kinase alpha or beta isoform.

In certain embodiments, a method is provided for selectively inhibiting a PI3 kinase gamma isoform over PI3 kinase delta isoform wherein the inhibition takes place in a cell. Non-limiting examples of the methods disclosed herein can comprise contacting PI3 kinase gamma isoform with an effective amount of a compound or a pharmaceutical composition disclosed herein. In an embodiment, such contact can occur in a cell.

In certain embodiments, a method is provided for selectively inhibiting a PI3 kinase gamma isoform over PI3 kinase delta isoform wherein the inhibition takes place in a subject suffering from a disorder selected from cancer, bone disorder, inflammatory disease, immune disease, nervous system disease (e.g., a neuropsychiatric disorder), metabolic disease, respiratory disease, thrombosis, and cardiac disease, said method comprising administering an effective amount of a compound or a pharmaceutical composition provided herein to said subject. In certain embodiments, provided herein is a method of treating a subject suffering from a disorder associated with PI3 kinase, said method comprising selectively modulating the PI3 kinase gamma isoform over PI3 kinase delta isoform by administering an amount of a compound or a pharmaceutical composition provided herein to said subject, wherein said amount is sufficient for selective modulation of PI3 kinase gamma isoform over PI3 kinase delta isoform.

In certain embodiments, provided herein is a method of inhibiting a PI3 kinase in a subject suffering from an inflammatory disease, an immune disease, or a respiratory disease, comprising administering to the subject an effective amount of a compound provided herein (e.g., a compound of Formula I). In one embodiment, the subject is a mammal. In one embodiment, the mammal is a human. In one embodiment, the subject is a human.

In some embodiments, the disorder suffered by the subject is a cancer. In one embodiment, the cancer is a hematological

cancer. In one embodiment, the cancer is acute myeloid leukemia (AML), chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS), myeloproliferative disorders, mast cell cancer, Hodgkin disease, non-Hodgkin lymphomas, diffuse large B-cell lymphoma, human lymphotrophic virus type 1 (HTLV-1) leukemia/lymphoma, AIDS-related lymphoma, adult T-cell lymphoma, acute lymphocytic leukemia (ALL), T-cell acute lymphocytic leukemia, B-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia, or multiple myeloma (MM). In one embodiment, the cancer is leukemia or lymphoma. In one embodiment, the leukemia is B-cell acute lymphoblastic leukemia (B-ALL), acute myeloid leukemia (AML), acute lymphocytic leukemia, chronic myeloid leukemia, hairy cell leukemia, myelodysplasia, myeloproliferative disorders, acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), multiple myeloma (MM), myelodysplastic syndrome (MDS), or mast cell cancer. In one embodiment, the lymphoma is diffuse large B-cell lymphoma, B-cell immunoblastic lymphoma, small non-cleaved cell lymphoma, human lymphotropic virus-type 1 (HTLV-1) leukemia/lymphoma, adult T-cell lymphoma, Hodgkin disease, or non-Hodgkin lymphomas.

In one embodiment, the cancer is a solid tumor. In one embodiment, the cancer is lung cancer, e.g., non-small cell lung cancer, small cell lung cancer; melanoma; prostate cancer; glioblastoma; endometrial cancer; pancreatic cancer; renal cell carcinoma; colorectal cancer; breast cancer; thyroid cancer; or ovarian cancer. In one embodiment, the solid tumor is prostate cancer, breast cancer, or glioblastomas.

In some embodiments, the disorder suffered by the subject is an inflammatory disease or an immune disease. In one embodiment, the inflammatory disease or the immune disease is asthma, emphysema, allergy, dermatitis, rheumatoid arthritis, psoriasis, lupus erythematosus, graft versus host disease, inflammatory bowel disease, eczema, scleroderma, Crohn's disease, or multiple sclerosis. In one embodiment, the disorder is rheumatoid arthritis. In one embodiment, the disorder is rheumatoid arthritis, and the amount of the compound is effective to ameliorate one or more symptoms associated with rheumatoid arthritis, wherein the symptom associated with rheumatoid arthritis is independently a reduction in the swelling of the joints, a reduction in serum anti collagen levels, a reduction in bone resorption, a reduction in cartilage damage, a reduction in pannus, or a reduction in inflammation.

In some embodiments, the disorder suffered by the subject is a respiratory disease. In one embodiment, the respiratory disease is asthma, chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, or bronchiectasis. In one embodiment, the disorder is asthma.

In one embodiment, the methods provided herein further comprise administration of one or more therapeutic agents selected from chemotherapeutic agents, cytotoxic agents, and radiation. In one embodiment, the compound is administered in combination with an mTOR inhibitor. In one embodiment, the compound is administered in combination with one or more of: an agent that inhibits IgE production or activity, 2-(4-(6-cyclohexyloxy-2-naphtyloxy)phenylacetamide)benzoic acid, an mTOR inhibitor, rapamycin, a TORC1 inhibitor, a TORC2 inhibitor, an anti-IgE antibody, prednisone, corticosteroid, a leukotriene inhibitor, XOLAIR, ADVAIR, SINGULAIR, or SPIRIVA. In one embodiment, the compound is administered in combination with one or more of: a mitotic inhibitor, an alkylating agent, an anti-metabolite, an intercalating antibiotic, a growth factor inhibitor, a cell cycle inhibitor, an enzyme, a topoisomerase inhibitor, an anti-hormone, an angiogenesis inhibitor, an anti-androgen, or an anti-receptor kinase antibody. In one embodiment, the compound is administered in combination with one or more of: Imatinib Mesylate, bortezomib, bicalutamide, gefitinib, ADRIAMYCIN, alkylating agents, alkyl sulfonates, ethylenimines, altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide, trimethylolomelamine, nitrogen mustards, chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, nitrosureas, antibiotics, anti-metabolites, denopterin, methotrexate, pteropterin, trimetrexate, 5-fluorouracil (5-FU), fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, androgens, anti-adrenals, folic acid replenisher, arabinoside, cyclophosphamide, thiotepa, taxanes, anti-hormonal agents, anti-estrogens, tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, onapristone, toremifene, anti-androgens, chlorambucil, gemcitabine, 6-thioguanine; mercaptopurine; cisplatin, carboplatin, vincristine; vinorelbine, vinblastin, ifosfamide, mitomycin C, daunorubicin, doxorubicin, mitoxantrone, HERCEPTIN, AVASTIN, ERBITUX, RITUXAN, TAXOL, ARIMIDEX, TAXOTERE, or an anti-receptor tyrosine kinase antibody selected from cetuximab, panitumumab, trastuzumab, anti CD20 antibody, rituximab, tositumomab, alemtuzumab, bevacizumab, and gemtuzumab. In one embodiment, the compound is administered in combination with one or more of: bortezomib, ADRIAMYCIN, alkylating agents, anti-metabolites, denopterin, pteropterin, trimetrexate, a nitrogen mustard, chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, methotrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, androgens, cyclophosphamide, taxanes, anti-hormonal agents, gemcitabine; cisplatin, carboplatin, vincristine, vinorelbine, vinblastin, ifosfamide, mitomycin C, daunorubicin, doxorubicin, mitoxantrone, HERCEPTIN, AVASTIN, ERBITUX, RITUXAN, TAXOL, ARIMIDEX, or TAXOTERE. In one embodiment, the compound is administered in combination with one or more of: non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, prednisone, chloroquine, hydroxychloroquine, azathioprine, cyclophosphamide, methotrexate, cyclosporine, anti-CD20 antibodies, ENBREL, REMICADE, HUMIRA, AVONEX, or REBIF.

In one embodiment, provided herein is a method of inhibiting a PI3 kinase in a subject suffering from a cancer, comprising administering to the subject an effective amount of a compound provided herein (e.g., a compound of Formula I). In one embodiment, the cancer is selected from acute myeloid leukemia (AML), chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS), myeloproliferative disorders, mast cell cancer, Hodgkin disease, non-Hodgkin lymphomas, diffuse large B-cell lymphoma, human lymphotrophic virus-type 1 (HTLV-1) leukemia/lymphoma, AIDS-related lymphoma, adult T-cell lymphoma, acute lymphocytic leukemia (ALL), B-cell acute lymphoblastic leukemia, T-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia, or multiple myeloma (MM). In one embodiment, the cancer is leukemia or lymphoma. In one embodiment, the leukemia is selected from B-cell acute lymphoblastic leukemia (B-ALL), acute lymphocytic leukemia, hairy cell leukemia, myelodys-

plasia, myeloproliferative disorders, acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), multiple myeloma (MM), myelodysplastic syndrome (MDS), or mast cell cancer. In one embodiment, the lymphoma is selected from diffuse large B-cell lymphoma, B-cell immunoblastic lymphoma, small non-cleaved cell lymphoma, human lymphotropic virus-type 1 (HTLV-1) leukemia/lymphoma, AIDS-related lymphoma, adult T-cell lymphoma, Hodgkin disease, or non-Hodgkin lymphomas. In one embodiment, the compound is administered in combination with one or more therapeutic agents provided herein.

In one embodiment, provided herein is a method of inhibiting a PI3 kinase in a subject suffering from an inflammatory disease or an immune disease, comprising administering to the subject an effective amount of a compound provided herein (e.g., a compound of Formula I). In one embodiment, the inflammatory disease or immune disease is asthma, emphysema, allergy, dermatitis, rheumatoid arthritis, psoriasis, lupus erythematosus, graft versus host disease, inflammatory bowel disease, eczema, scleroderma, Crohn's disease, or multiple sclerosis. In one embodiment, the inflammatory disease or immune disease is rheumatoid arthritis. In one embodiment, the compound is administered in combination with one or more therapeutic agents provided herein.

In one embodiment, provided herein is a method of inhibiting a PI3 kinase in a subject suffering from a respiratory disease, comprising administering to the subject an effective amount of a compound provided herein (e.g., a compound of Formula I). In one embodiment, the respiratory disease is asthma, chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, or bronchiectasis. In one embodiment, the respiratory disease is asthma. In one embodiment, the compound is administered in combination with one or more therapeutic agents provided herein.

In certain embodiments, provided herein is a method of inhibiting PI3K-γ in a subject, comprising administering to the subject an effective amount of a compound provided herein (e.g., a compound of Formula I).

In certain embodiments, provided herein is a method of inhibiting PI3K-δ in a subject, comprising administering to the subject an effective amount of a compound provided herein (e.g., a compound of Formula I).

In certain embodiments, provided herein is a method of making a compound described herein.

In certain embodiments, provided herein is a reaction mixture comprising a compound described herein.

In certain embodiments, provided herein is a kit comprising a compound described herein.

In some embodiments, a method is provided for treating a disease or disorder described herein, the method comprising administering a therapeutically effective amount of a compound or a pharmaceutical composition described herein to a subject.

In some embodiments, a method is provided for treating a PI3K mediated disorder in a subject, the method comprising administering a therapeutically effective amount of a compound or a pharmaceutical composition described herein to a subject.

In some embodiments, provided herein is a use of a compound or a pharmaceutical composition described herein for the treatment of a disease or disorder described herein in a subject.

In some embodiments, provided herein is a use of a compound or a pharmaceutical composition described herein for the treatment of a PI3K mediated disorder in a subject.

In some embodiments, provided herein is a use of a compound or a pharmaceutical composition described herein in the manufacture of a medicament for the treatment of a disease or disorder described herein in a subject.

In some embodiments, provided herein is use of a compound or a pharmaceutical composition described herein in the manufacture of a medicament for the treatment of a PI3K mediated disorder in a subject.

INCORPORATION BY REFERENCE

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

DETAILED DESCRIPTION

In one embodiment, provided are heterocyclyl compounds, and pharmaceutically acceptable forms thereof, including, but not limited to, salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives thereof.

In another embodiment, provided are methods of treating and/or managing various diseases and disorders, which comprises administering to a patient a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable form (e.g., salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof. Examples of diseases and disorders are described herein.

In another embodiment, provided are methods of preventing various diseases and disorders, which comprises administering to a patient in need of such prevention a prophylactically effective amount of a compound provided herein, or a pharmaceutically acceptable form (e.g., salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof. Examples of diseases and disorders are described herein.

In other embodiments, a compound provided herein, or a pharmaceutically acceptable form (e.g., salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, is administered in combination with another drug ("second active agent") or treatment. Second active agents include small molecules and large molecules (e.g., proteins and antibodies), examples of which are provided herein, as well as stem cells. Other methods or therapies that can be used in combination with the administration of compounds provided herein include, but are not limited to, surgery, blood transfusions, immunotherapy, biological therapy, radiation therapy, and other non-drug based therapies presently used to treat, prevent or manage various disorders described herein.

Also provided are pharmaceutical compositions (e.g., single unit dosage forms) that can be used in the methods provided herein. In one embodiment, pharmaceutical compositions comprise a compound provided herein, or a pharmaceutically acceptable form (e.g., salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, and optionally one or more second active agents.

While specific embodiments have been discussed, the specification is illustrative only and not restrictive. Many variations of this disclosure will become apparent to those skilled in the art upon review of this specification.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this specification pertains.

As used in the specification and claims, the singular form "a", "an" and "the" includes plural references unless the context clearly dictates otherwise.

As used herein, and unless otherwise indicated, the term "about" or "approximately" means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term "about" or "approximately" means within 1, 2, 3, or 4 standard deviations. In certain embodiments, the term "about" or "approximately" means within 50%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range.

As used herein, "agent" or "biologically active agent" or "second active agent" refers to a biological, pharmaceutical, or chemical compound or other moiety. Non-limiting examples include simple or complex organic or inorganic molecules, a peptide, a protein, an oligonucleotide, an antibody, an antibody derivative, an antibody fragment, a vitamin, a vitamin derivative, a carbohydrate, a toxin, or a chemotherapeutic compound, and metabolites thereof. Various compounds can be synthesized, for example, small molecules and oligomers (e.g., oligopeptides and oligonucleotides), and synthetic organic compounds based on various core structures. In addition, various natural sources can provide compounds for screening, such as plant or animal extracts, and the like. A skilled artisan can readily recognize that there is no limit as to the structural nature of the agents of this disclosure.

The term "agonist" as used herein refers to a compound or agent having the ability to initiate or enhance a biological function of a target protein or polypeptide, such as increasing the activity or expression of the target protein or polypeptide. Accordingly, the term "agonist" is defined in the context of the biological role of the target protein or polypeptide. While some agonists herein specifically interact with (e.g., bind to) the target, compounds and/or agents that initiate or enhance a biological activity of the target protein or polypeptide by interacting with other members of the signal transduction pathway of which the target polypeptide is a member are also specifically included within this definition.

The terms "antagonist" and "inhibitor" are used interchangeably, and they refer to a compound or agent having the ability to inhibit a biological function of a target protein or polypeptide, such as by inhibiting the activity or expression of the target protein or polypeptide. Accordingly, the terms "antagonist" and "inhibitor" are defined in the context of the biological role of the target protein or polypeptide. While some antagonists herein specifically interact with (e.g., bind to) the target, compounds that inhibit a biological activity of the target protein or polypeptide by interacting with other members of the signal transduction pathway of which the target protein or polypeptide are also specifically included within this definition. Non-limiting examples of biological activity inhibited by an antagonist include those associated with the development, growth, or spread of a tumor, or an undesired immune response as manifested in autoimmune disease.

An "anti-cancer agent", "anti-tumor agent" or "chemotherapeutic agent" refers to any agent useful in the treatment of a neoplastic condition. One class of anti-cancer agents comprises chemotherapeutic agents. "Chemotherapy" means the administration of one or more chemotherapeutic drugs and/or other agents to a cancer patient by various methods, including intravenous, oral, intramuscular, intraperitoneal, intravesical, subcutaneous, transdermal, or buccal administration, or inhalation, or in the form of a suppository.

The term "cell proliferation" refers to a phenomenon by which the cell number has changed as a result of division. This term also encompasses cell growth by which the cell morphology has changed (e.g., increased in size) consistent with a proliferative signal.

The term "co-administration," "administered in combination with," and their grammatical equivalents, as used herein, encompass administration of two or more agents to subject so that both agents and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which both agents are present.

The term "effective amount" or "therapeutically effective amount" refers to that amount of a compound or pharmaceutical composition described herein that is sufficient to effect the intended application including, but not limited to, disease treatment, as illustrated below. The therapeutically effective amount can vary depending upon the intended application (in vitro or in vivo), or the subject and disease condition being treated, e.g., the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, e.g., reduction of platelet adhesion and/or cell migration. The specific dose will vary depending on, for example, the particular compounds chosen, the dosing regimen to be followed, whether it is administered in combination with other agents, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

As used herein, the terms "treatment", "treating", "palliating" and "ameliorating" are used interchangeably herein. These terms refer to an approach for obtaining beneficial or desired results including, but not limited to, therapeutic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient can still be afflicted with the underlying disorder.

As used herein, the terms "prevention" and "preventing" are used herein to refer to an approach for obtaining beneficial or desired results including, but not limited, to prophylactic benefit. For prophylactic benefit, the pharmaceutical compositions can be administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

A "therapeutic effect," as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described above. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

"Signal transduction" is a process during which stimulatory or inhibitory signals are transmitted into and within a cell to elicit an intracellular response. A "modulator" of a signal transduction pathway refers to a compound which modulates the activity of one or more cellular proteins mapped to the same specific signal transduction pathway. A modulator can augment (agonist) or suppress (antagonist) the activity of a signaling molecule.

The term "selective inhibition" or "selectively inhibit" as applied to a biologically active agent refers to the agent's

ability to selectively reduce the target signaling activity as compared to off-target signaling activity, via direct or indirect interaction with the target. For example, a compound that selectively inhibits one isoform of PI3K over another isoform of PI3K has an activity of at least greater than about 1× against a first isoform relative to the compound's activity against the second isoform (e.g., at least about 2×, 3×, 5×, 10×, 20×, 50×, 100×, 200×, 500×, or 1000×). In certain embodiments, these terms refer to (1) a compound of described herein that selectively inhibits the gamma isoform over the alpha, beta, or delta isoform; or (2) a compound described herein that selectively inhibits the delta isoform over the alpha or beta isoform. By way of non-limiting example, the ratio of selectivity can be greater than a factor of about 1, greater than a factor of about 2, greater than a factor of about 3, greater than a factor of about 5, greater than a factor of about 10, greater than a factor of about 50, greater than a factor of about 100, greater than a factor of about 200, greater than a factor of about 400, greater than a factor of about 600, greater than a factor of about 800, greater than a factor of about 1000, greater than a factor of about 1500, greater than a factor of about 2000, greater than a factor of about 5000, greater than a factor of about 10,000, or greater than a factor of about 20,000, where selectivity can be measured by ratio of IC_{50} values, which in turn can be measured by, e.g., in vitro or in vivo assays such as those described in Examples described herein. In one embodiment, the selectivity of a first PI3K isoform over a second PI3K isoform is measured by the ratio of the IC_{50} value against the second PI3K isoform to the IC_{50} value against the first PI3K gamma isoform. For example, a delta/gamma selectivity ratio of a compound can be measured by the ratio of the compound's inhibitory activity against the delta isoform in terms of IC_{50} or the like to the compound's inhibitory activity against the gamma isoform in terms of IC_{50} or the like. If the delta/gamma selectivity ratio is larger than 1, the compound selectively inhibits the gamma isoform over the delta isoform. In certain embodiments, the PI3K gamma isoform IC_{50} activity of a compound of provided herein can be less than about 1000 nM, less than about 500 nM, less than about 400 nM, less than about 300 nM, less than about 200 nM, less than about 100 nM, less than about 75 nM, less than about 50 nM, less than about 25 nM, less than about 20 nM, less than about 15 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM. In certain embodiments, the PI3K delta isoform IC_{50} activity of a compound provided herein can be less than about 1000 nM, less than about 500 nM, less than about 400 nM, less than about 300 nM, less than about 200 nM, less than about 100 nM, less than about 75 nM, less than about 50 nM, less than about 25 nM, less than about 20 nM, less than about 15 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM.

"Radiation therapy" means exposing a patient, using routine methods and compositions known to the practitioner, to radiation emitters such as, but not limited to, alpha-particle emitting radionuclides (e.g., actinium and thorium radionuclides), low linear energy transfer (LET) radiation emitters (e.g., beta emitters), conversion electron emitters (e.g., strontium-89 and samarium-153-EDTMP), or high-energy radiation, including without limitation x-rays, gamma rays, and neutrons.

"Subject" to which administration is contemplated includes, but is not limited to, humans (e.g., a male or female of any age group, e.g., a pediatric subject (e.g., infant, child, adolescent) or adult subject (e.g., young adult, middle-aged adult or senior adult)) and/or other primates (e.g., cynomolgus monkeys, rhesus monkeys); mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs; and/or birds, including commercially relevant birds such as chickens, ducks, geese, quail, and/or turkeys.

The term "in vivo" refers to an event that takes place in a subject's body.

The term "in vitro" refers to an event that takes places outside of a subject's body. For example, an in vitro assay encompasses any assay conducted outside of a subject. In vitro assays encompass cell-based assays in which cells, alive or dead, are employed. In vitro assays also encompass a cell-free assay in which no intact cells are employed.

As used herein, "pharmaceutically acceptable esters" include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, aralkyl, and cycloalkyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfonic acids, sulfuric acids, and boronic acids.

As used herein, "pharmaceutically acceptable enol ethers" include, but are not limited to, derivatives of formula —C═C(OR) where R can be selected from alkyl, alkenyl, alkynyl, aryl, aralkyl, and cycloalkyl. Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula —C═C(OC(O)R) where R can be selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, and cycloalkyl.

As used herein, a "pharmaceutically acceptable form" of a disclosed compound includes, but is not limited to, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives of disclosed compounds. In one embodiment, a "pharmaceutically acceptable form" includes, but is not limited to, pharmaceutically acceptable salts, isomers, prodrugs and isotopically labeled derivatives of disclosed compounds.

In certain embodiments, the pharmaceutically acceptable form is a pharmaceutically acceptable salt. As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of subjects without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge et al. describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* (1977) 66:1-19. Pharmaceutically acceptable salts of the compounds provided herein include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, besylate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, naphthalene-m,n-bissulfonates, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. In some embodiments, organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid,

succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, naphthalene-m,n-bissulfonic acids and the like.

Pharmaceutically acceptable salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

In certain embodiments, the pharmaceutically acceptable form is a solvate (e.g., a hydrate). As used herein, the term "solvate" refers to compounds that further include a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. The solvate can be of a disclosed compound or a pharmaceutically acceptable salt thereof. Where the solvent is water, the solvate is a "hydrate". Pharmaceutically acceptable solvates and hydrates are complexes that, for example, can include 1 to about 100, or 1 to about 10, or one to about 2, about 3 or about 4, solvent or water molecules. It will be understood that the term "compound" as used herein encompasses the compound and solvates of the compound, as well as mixtures thereof.

In certain embodiments, the pharmaceutically acceptable form is a prodrug. As used herein, the term "prodrug" refers to compounds that are transformed in vivo to yield a disclosed compound or a pharmaceutically acceptable form of the compound. A prodrug can be inactive when administered to a subject, but is converted in vivo to an active compound, for example, by hydrolysis (e.g., hydrolysis in blood). In certain cases, a prodrug has improved physical and/or delivery properties over the parent compound. Prodrugs are typically designed to enhance pharmaceutically and/or pharmacokinetically based properties associated with the parent compound. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, e.g., Bundgard, H., *Design of Prodrugs* (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam). A discussion of prodrugs is provided in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," *A.C.S. Symposium Series*, Vol. 14, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein. Exemplary advantages of a prodrug can include, but are not limited to, its physical properties, such as enhanced water solubility for parenteral administration at physiological pH compared to the parent compound, or it enhances absorption from the digestive tract, or it can enhance drug stability for long-term storage.

The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound in vivo when such prodrug is administered to a subject. Prodrugs of an active compound, as described herein, can be prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of an alcohol or acetamide, formamide and benzamide derivatives of an amine functional group in the active compound and the like. Other examples of prodrugs include compounds that comprise —NO, —NO_2, —ONO, or —ONO_2 moieties. Prodrugs can typically be prepared using well-known methods, such as those described in *Burger's Medicinal Chemistry and Drug Discovery,* 172-178, 949-982 (Manfred E. Wolff ed., 5th ed., 1995), and *Design of Prodrugs* (H. Bundgaard ed., Elsevier, New York, 1985).

For example, if a disclosed compound or a pharmaceutically acceptable form of the compound contains a carboxylic acid functional group, a prodrug can comprise a pharmaceutically acceptable ester formed by the replacement of the hydrogen atom of the acid group with a group such as (C_1-C_8)alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N—(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di(C_1-C_2)alkylcarbamoyl-(C_1-C_2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl.

Similarly, if a disclosed compound or a pharmaceutically acceptable form of the compound contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl (C_1-C_6)alkoxycarbonyloxymethyl, N—(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanoyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from naturally occurring L-amino acids, P(O)(OH)$_2$, —P(O)(O(C_1-C_6)alkyl)$_2$, and glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

If a disclosed compound or a pharmaceutically acceptable form of the compound incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C_1-C_{10})alkyl, (C_3-C_7)cycloalkyl, benzyl, a natural α-aminoacyl or natural α-aminoacyl-natural α-aminoacyl, —C(OH)C(O)OY^1 wherein Y^1 is H, (C_1-C_6) alkyl or benzyl, —C(OY^2)Y^3 wherein Y^2 is (C_1-C_4)alkyl and Y^3 is (C_1-C_6)alkyl, carboxy(C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N— or di-N,N—(C_1-C_6)alkylaminoalkyl, —C(Y^4)Y^5 wherein Y^4 is H or methyl and Y^5 is mono-N— or di-N, N—(C_1-C_6)alkylamino, morpholino, piperidin-1-yl or pyrrolidin-1-yl.

In certain embodiments, the pharmaceutically acceptable form is an isomer. "Isomers" are different compounds that have the same molecular formula. "Atropisomers" are stereoisomers from hindered rotation about single bonds and can

be resolved or isolated by methods known to those skilled in the art. For example, certain B substituents of a compound of Formula (I) provided herein with ortho or meta substituted phenyl may form atropisomers, where they may be separated and isolated.

"Stereoisomers" are isomers that differ only in the way the atoms are arranged in space. As used herein, the term "isomer" includes any and all geometric isomers and stereoisomers. For example, "isomers" include geometric double bond cis- and trans-isomers, also termed E- and Z-isomers; R- and S-enantiomers; diastereomers, (d)-isomers and (l)-isomers, racemic mixtures thereof; and other mixtures thereof, as falling within the scope of this disclosure.

In certain embodiments, the symbol ------ denotes a bond that can be a single or double as described herein.

In certain embodiments, provided herein are various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a carbocyclic ring. Substituents around a carbon-carbon double bond are designated as being in the "Z" or "E" configuration wherein the terms "Z" and "E" are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the "E" and "Z" isomers.

Substituents around a carbon-carbon double bond alternatively can be referred to as "cis" or "trans," where "cis" represents substituents on the same side of the double bond and "trans" represents substituents on opposite sides of the double bond. The arrangement of substituents around a carbocyclic ring can also be designated as "cis" or "trans." The term "cis" represents substituents on the same side of the plane of the ring, and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of the plane of the ring are designated "cis/trans."

"Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A mixture of a pair of enantiomers in any proportion can be known as a "racemic" mixture. The term "(±)" is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry can be specified according to the Cahn-Ingold-Prelog R-S system. When a compound is an enantiomer, the stereochemistry at each chiral carbon can be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (−) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry at each asymmetric atom, as (R)- or (S)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers, including racemic mixtures, optically substantially pure forms and intermediate mixtures. Optically active (R)- and (S)-isomers can be prepared, for example, using chiral synthons or chiral reagents, or resolved using conventional techniques.

The "enantiomeric excess" or "% enantiomeric excess" of a composition can be calculated using the equation shown below. In the example shown below, a composition contains 90% of one enantiomer, e.g., an S enantiomer, and 10% of the other enantiomer, e.g., an R enantiomer.

$$ee=(90-10)/100=80\%.$$

Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%. Some compositions described herein contain an enantiomeric excess of at least about 1%, about 5%, about 10%, about 20%, about 30%, about 40%, about 50%, about 75%, about 90%, about 95%, or about 99% of the S enantiomer. In other words, the compositions contain an enantiomeric excess of the S enantiomer over the R enantiomer. In other embodiments, some compositions described herein contain an enantiomeric excess of at least about 1%, about 5%, about 10%, about 20%, about 30%, about 40%, about 50%, about 75%, about 90%, about 95%, or about 99% of the R enantiomer. In other words, the compositions contain an enantiomeric excess of the R enantiomer over the S enantiomer.

For instance, an isomer/enantiomer can, in some embodiments, be provided substantially free of the corresponding enantiomer, and can also be referred to as "optically enriched," "enantiomerically enriched," "enantiomerically pure" and "non-racemic," as used interchangeably herein. These terms refer to compositions in which the amount of one enantiomer is greater than the amount of that one enantiomer in a control mixture of the racemic composition (e.g., greater than 1:1 by weight). For example, an enantiomerically enriched preparation of the S enantiomer, means a preparation of the compound having greater than about 50% by weight of the S enantiomer relative to the total weight of the preparation (e.g., total weight of S and R isomers). such as at least about 75% by weight, further such as at least about 80% by weight. In some embodiments, the enrichment can be much greater than about 80% by weight, providing a "substantially enantiomerically enriched," "substantially enantiomerically pure" or a "substantially non-racemic" preparation, which refers to preparations of compositions which have at least about 85% by weight of one enantiomer relative to the total weight of the preparation, such as at least about 90% by weight, and further such as at least about 95% by weight. In certain embodiments, the compound provided herein is made up of at least about 90% by weight of one enantiomer. In other embodiments, the compound is made up of at least about 95%, about 98%, or about 99% by weight of one enantiomer.

In some embodiments, the compound is a racemic mixture of (S)- and (R)-isomers. In other embodiments, provided herein is a mixture of compounds wherein individual compounds of the mixture exist predominately in an (S)- or (R)-isomeric configuration. For example, in some embodiments, the compound mixture has an (S)-enantiomeric excess of greater than about 10%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 55%, greater than about 60%, greater than about 65%, greater than about 70%, greater than about 75%, greater than about 80%, greater than about 85%, greater than about 90%, greater than about 95%, greater than about 96%, greater than about 97%, greater than about 98%, or greater than about 99%. In some embodiments, the compound mixture has an (S)-enantiomeric excess of about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 99.5%, or more. In some embodiments, the compound mixture has an (S)-enantiomeric excess of about 55% to about 99.5%, about 60% to about 99.5%, about 65% to about 99.5%, about 70% to about 99.5%, about 75% to about 99.5%, about 80% to about 99.5%, about 85% to

about 99.5%, about 90% to about 99.5%, about 95% to about 99.5%, about 96% to about 99.5%, about 97% to about 99.5%, about 98% to about 99.5%, or about 99% to about 99.5%, or more than about 99.5%.

In other embodiments, the compound mixture has an (R)-enantiomeric excess of greater than about 10%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 55%, greater than about 60%, greater than about 65%, greater than about 70%, greater than about 75%, greater than about 80%, greater than about 85%, greater than about 90%, greater than about 95%, greater than about 96%, greater than about 97%, greater than about 98%, or greater than about 99%. In some embodiments, the compound mixture has an (R)-enantiomeric excess of about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 99.5%, or more. In some embodiments, the compound mixture has an (R)-enantiomeric excess of about 55% to about 99.5%, about 60% to about 99.5%, about 65% to about 99.5%, about 70% to about 99.5%, about 75% to about 99.5%, about 80% to about 99.5%, about 85% to about 99.5%, about 90% to about 99.5%, about 95% to about 99.5%, about 96% to about 99.5%, about 97% to about 99.5%, about 98% to about 99.5%, or about 99% to about 99.5%, or more than about 99.5%.

In other embodiments, the compound mixture contains identical chemical entities except for their stereochemical orientations, namely (S)- or (R)-isomers. For example, if a compound disclosed herein has —CH(R)— unit, and R is not hydrogen, then the —CH(R)— is in an (S)- or (R)-stereochemical orientation for each of the identical chemical entities (i.e., (S)- or (R)-stereoisomers). In some embodiments, the mixture of identical chemical entities (i.e., mixture of stereoisomers) is a racemic mixture of (S)- and (R)-isomers. In another embodiment, the mixture of the identical chemical entities (i.e., mixture of stereoisomers) contains predominately (S)-isomer or predominately (R)-isomer. For example, in some embodiments, the (S)-isomer in the mixture of identical chemical entities (i.e., mixture of stereoisomers) is present at about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 99.5% by weight, or more, relative to the total weight of the mixture of (S)- and (R)-isomers. In some embodiments, the (S)-isomer in the mixture of identical chemical entities (i.e., mixture of stereoisomers) is present at an (S)-enantiomeric excess of about 10% to about 99.5%, about 20% to about 99.5%, about 30% to about 99.5%, about 40% to about 99.5%, about 50% to about 99.5%, about 55% to about 99.5%, about 60% to about 99.5%, about 65% to about 99.5%, about 70% to about 99.5%, about 75% to about 99.5%, about 80% to about 99.5%, about 85% to about 99.5%, about 90% to about 99.5%, about 95% to about 99.5%, about 96% to about 99.5%, about 97% to about 99.5%, about 98% to about 99.5%, or about 99% to about 99.5%, or more than about 99.5%.

In other embodiments, the (R)-isomer in the mixture of identical chemical entities (i.e., mixture of stereoisomers) is present at about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 99.5% by weight, or more, relative to the total weight of the mixture of (S)- and (R)-isomers. In some embodiments, the (R)-isomers in the mixture of identical chemical entities (i.e., mixture of stereoisomers) is present at an (R)-enantiomeric excess of about 10% to about 99.5%, about 20% to about 99.5%, about 30% to about 99.5%, about 40% to about 99.5%, about 50% to about 99.5%, about 55% to about 99.5%, about 60% to about 99.5%, about 65% to about 99.5%, about 70% to about 99.5%, about 75% to about 99.5%, about 80% to about 99.5%, about 85% to about 99.5%, about 90% to about 99.5%, about 95% to about 99.5%, about 96% to about 99.5%, about 97% to about 99.5%, about 98% to about 99.5%, or about 99% to about 99.5%, or more than about 99.5%.

Enantiomers can be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC), the formation and crystallization of chiral salts, or prepared by asymmetric syntheses. See, for example, *Enantiomers, Racemates and Resolutions* (Jacques, Ed., Wiley Interscience, New York, 1981); Wilen et al., *Tetrahedron* 33:2725 (1977); *Stereochemistry of Carbon Compounds* (E. L. Eliel, Ed., McGraw-Hill, NY, 1962); and *Tables of Resolving Agents and Optical Resolutions* p. 268 (E. L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, Ind. 1972).

In certain embodiments, the pharmaceutically acceptable form is a tautomer. As used herein, the term "tautomer" is a type of isomer that includes two or more interconvertable compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency (e.g., a single bond to a double bond, a triple bond to a double bond, or a triple bond to a single bond, or vice versa). "Tautomerization" includes prototropic or proton-shift tautomerization, which is considered a subset of acid-base chemistry. "Prototropic tautomerization" or "proton-shift tautomerization" involves the migration of a proton accompanied by changes in bond order. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Where tautomerization is possible (e.g., in solution), a chemical equilibrium of tautomers can be reached. Tautomerizations (i.e., the reaction providing a tautomeric pair) can be catalyzed by acid or base, or can occur without the action or presence of an external agent. Exemplary tautomerizations include, but are not limited to, keto-enol; amide-imide; lactam-lactim; enamine-imine; and enamine-(a different) enamine tautomerizations. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. A specific example of phenol-keto tautomerization is the interconversion of pyridin-4-ol and pyridin-4(1H)-one tautomers.

Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement or enrichment of a hydrogen by deuterium or tritium at one or more atoms in the molecule, or the replacement or enrichment of a carbon by ^{13}C or ^{14}C at one or more atoms in the molecule, are within the scope of this disclosure. In one embodiment, provided herein are isotopically labeled compounds having one or more hydrogen atoms replaced by or enriched by deuterium. In one embodiment, provided herein are isotopically labeled compounds having one or more hydrogen atoms replaced by or enriched by tritium. In one embodiment, provided herein are isotopically labeled compounds having one or more carbon atoms replaced or enriched by ^{13}C. In one embodiment, provided herein are isotopically labeled compounds having one or more carbon atoms replaced or enriched by ^{14}C.

The disclosure also embraces isotopically labeled compounds which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic

mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, and chlorine, such as, e.g., ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Certain isotopically-labeled disclosed compounds (e.g., those labeled with ^{3}H and/or ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes can allow for ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) can afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements). Isotopically labeled disclosed compounds can generally be prepared by substituting an isotopically labeled reagent for a non-isotopically labeled reagent. In some embodiments, provided herein are compounds that can also contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. All isotopic variations of the compounds as disclosed herein, whether radioactive or not, are encompassed within the scope of the present disclosure.

"Pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions as disclosed herein is contemplated. Supplementary active ingredients can also be incorporated into the pharmaceutical compositions.

Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March *March's Advanced Organic Chemistry,* 5th ed., John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, Some *Modern Methods of Organic Synthesis,* 3rd ed., Cambridge University Press, Cambridge, 1987.

When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example "C_{1-6} alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having, in some embodiments, from one to ten carbon atoms (e.g., C_1-C_{10} alkyl). Linear or straight alkyl refers to an alkyl with no branching, e.g., methyl, ethyl, n-propyl. Whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range; e.g., "1 to 10 carbon atoms" means that the alkyl group can consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, etc., up to and including 10 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated. In some embodiments, an alkyl is a C_1-C_6 alkyl group. In some embodiments, alkyl groups have 1 to 10, 1 to 6, 1 to 4, or 1 to 3 carbon atoms. Representative saturated straight chain alkyls include, but are not limited to, -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, and -n-hexyl; while saturated branched alkyls include, but are not limited to, -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, 2-methylbutyl, 3-methylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylbutyl, and the like. The alkyl is attached to the parent molecule by a single bond. Unless stated otherwise in the specification, an alkyl group is optionally substituted by one or more of substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $—Si(R^a)_3$, $—OR^a$, $—SR^a$, $—OC(O)—R^a$, $—N(R^a)_2$, $—C(O)R^a$, $—C(O)OR^a$, $—OC(O)N(R^a)_2$, $—C(O)N(R^a)_2$, $—N(R^a)C(O)OR^a$, $—N(R^a)C(O)R^a$, $N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $—N(R^a)S(O)_tR^a$ (where t is 1 or 2), $—S(O)_tOR^a$ (where t is 1 or 2), $—S(O)_tN(R^a)_2$ (where t is 1 or 2), or $—O—P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

"Perhaloalkyl" refers to an alkyl group in which all of the hydrogen atoms have been replaced with a halogen selected from fluoro, chloro, bromo, and iodo. In some embodiments, all of the hydrogen atoms are each replaced with fluoro. In some embodiments, all of the hydrogen atoms are each replaced with chloro. Examples of perhaloalkyl groups include $—CF_3$, $—CF_2CF_3$, $—CF_2CF_2CF_3$, $—CCl_3$, $—CFCl_2$, $—CF_2Cl$ and the like. "Haloalkyl" refers to an alkyl group in which one or more of the hydrogen atoms have been replaced with a halogen independently selected from fluoro, chloro, bromo, and iodo.

"Alkyl-cycloalkyl" refers to an -(alkyl)cycloalkyl radical where alkyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for alkyl and cycloalkyl respectively. The "alkyl-cycloalkyl" is bonded to the parent molecular structure through the alkyl group. The terms "alkenyl-cycloalkyl" and "alkynyl-cycloalkyl" mirror the above description of "alkyl-cycloalkyl" wherein the term "alkyl" is replaced with "alkenyl" or "alkynyl" respectively, and "alkenyl" or "alkynyl" are as described herein.

"Alkylaryl" refers to an -(alkyl)aryl radical where aryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively. The "alkylaryl" is bonded to the parent molecular structure through the alkyl group. The terms "-(alkenyl)aryl" and "-(alkynyl)aryl" mirror the above description of "-(alkyl)aryl" wherein the term "alkyl" is replaced with "alkenyl" or "alkynyl" respectively, and "alkenyl" or "alkynyl" are as described herein.

"Alkyl-heteroaryl" refers to an -(alkyl)heteroaryl radical where heteroaryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroaryl and alkyl respectively. The "alkyl-heteroaryl" is bonded to the parent molecular structure through the alkyl group. The terms "-(alkenyl)heteroaryl" and "-(alkynyl)heteroaryl" mirror the above description of "-(alkyl)heteroaryl" wherein the term

"alkyl" is replaced with "alkenyl" or "alkynyl" respectively, and "alkenyl" or "alkynyl" are as described herein.

"Alkyl-heterocyclyl" refers to an -(alkyl)heterocyclyl radical where alkyl and heterocyclyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocyclyl and alkyl respectively. The "alkyl-heterocyclyl" is bonded to the parent molecular structure through the alkyl group. The terms "-(alkenyl)heterocyclyl" and "-(alkynyl)heterocyclyl" mirror the above description of "-(alkyl)heterocyclyl" wherein the term "alkyl" is replaced with "alkenyl" or "alkynyl" respectively, and "alkenyl" or "alkynyl" are as described herein.

"Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double bond, and in some embodiments, having from two to ten carbon atoms (i.e., C_2-C_{10} alkenyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range; e.g., "2 to 10 carbon atoms" means that the alkenyl group can consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, etc., up to and including 10 carbon atoms. In certain embodiments, an alkenyl comprises two to eight carbon atoms. In other embodiments, an alkenyl comprises two to five carbon atoms (e.g., C_2-C_5 alkenyl). The alkenyl is attached to the parent molecular structure by a single bond, for example, ethenyl (i.e., vinyl), prop-1-enyl (i.e., allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C_{2-4} alkenyl groups include ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4) and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Unless stated otherwise in the specification, an alkenyl group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $—Si(R^a)_3$, $—OR^a$, $—SR^a$, $—OC(O)—R^a$, $—N(R^a)_2$, $—C(O)R^a$, $—C(O)OR^a$, $—OC(O)N(R^a)_2$, $C(O)N(R^a)_2$, $—N(R^a)C(O)OR^a$, $—N(R^a)C(O)R^a$, $—N(R^a)C(O)N(R^a)_2$, $—N(R^a)C(NR^a)N(R^a)_2$, $—N(R^a)S(O)_t R^a$ (where t is 1 or 2), $—S(O)_tOR^a$ (where t is 1 or 2), $—S(O)_tN(R^a)_2$ (where t is 1 or 2), or $—O—P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

"Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having, in some embodiments, from two to ten carbon atoms (i.e., C_2-C_{10} alkynyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range; e.g., "2 to 10 carbon atoms" means that the alkynyl group can consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, etc., up to and including 10 carbon atoms. In certain embodiments, an alkynyl comprises two to eight carbon atoms. In other embodiments, an alkynyl has two to five carbon atoms (e.g., C_2-C_5 alkynyl). The alkynyl is attached to the parent molecular structure by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise in the specification, an alkynyl group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $—Si(R^a)_3$, $—OR^a$, $—SR^a$, $—OC(O)—R^a$, $—N(R^a)_2$, $—C(O)R^a$, $—C(O)OR^a$, $—OC(O)N(R^a)_2$, $—C(O)N(R^a)_2$, $—N(R^a)C(O)OR^a$, $—N(R^a)C(O)R^a$, $—N(R^a)C(O)N(R^a)_2$, $—N(R^a)C(NR^a)N(R^a)_2$, $—N(R^a)S(O)_tR^a$ (where t is 1 or 2), $—S(O)_tOR^a$ (where t is 1 or 2), $—S(O)_tN(R^a)_2$ (where t is 1 or 2), or $—O—P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein. The terms "alkenoxy" and "alkynoxy" mirror the above description of "alkoxy" wherein the prefix "alk" is replaced with "alken" or "alkyn" respectively, and the parent "alkenyl" or "alkynyl" terms are as described herein.

The term "alkoxy" refers to the group —O-alkyl (in some embodiments, including from 1 to 10 carbon atoms), of a straight, branched, cyclic configuration and combinations thereof, attached to the parent molecular structure through an oxygen. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like. "Lower alkoxy" refers to alkoxy groups containing one to six carbons. In some embodiments, C_1-C_4 alkoxy is an alkoxy group which encompasses both straight and branched chain alkyls of from 1 to 4 carbon atoms. Unless stated otherwise in the specification, an alkoxy group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $—Si(R^a)_3$, $—OR^a$, $—OC(O)—R^a$, $—N(R^a)_2$, $—C(O)R^a$, $—C(O)OR^a$, $—OC(O)N(R^a)_2$, $—C(O)N(R^a)_2$, $—N(R^a)C(O)OR^a$, $—N(R^a)C(O)R^a$, $N(R^a)C(O)N(R^a)_2$, $—N(R^a)C(NR^a)N(R^a)_2$, $—N(R^a)S(O)_tR^a$ (where t is 1 or 2), $—S(O)_tOR^a$ (where t is 1 or 2), $—S(O)_tN(R^a)_2$ (where t is 1 or 2), or $—O—P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein. The terms "alkenoxy" and "alkynoxy" mirror the above description of "alkoxy" wherein the prefix "alk" is replaced with "alken" or "alkyn" respectively, and the parent "alkenyl" or "alkynyl" terms are as described herein.

The term "alkoxycarbonyl" refers to a group of the formula (alkoxy)(C=O)— attached to the parent molecular structure through the carbonyl carbon (in some embodiments, having from 1 to 10 carbon atoms). Thus a C_1-C_6 alkoxycarbonyl group comprises an alkoxy group having from 1 to 6 carbon atoms attached through its oxygen to a carbonyl linker. The C_1-C_6 designation does not include the carbonyl carbon in the atom count. "Lower alkoxycarbonyl" refers to an alkoxycarbonyl group wherein the alkyl portion of the alkoxy group is a lower alkyl group. In some embodiments, C_1-C_4 alkoxycar-

bonyl comprises an alkoxy group which encompasses both straight and branched chain alkoxy groups of from 1 to 4 carbon atoms. Unless stated otherwise in the specification, an alkoxycarbonyl group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, —$Si(R^a)_3$, —OR^a, —$OC(O)—R^a$, —$N(R^a)_2$, —$C(O)R^a$, —$C(O)OR^a$, —$OC(O)N(R^a)_2$, —$C(O)N(R^a)_2$, —$N(R^a)C(O)OR^a$, —$N(R^a)C(O)R^a$, —$N(R^a)C(O)N(R^a)_2$, —$N(R^a)C(NR^a)N(R^a)_2$, —$N(R^a)S(O)_1R^a$ (where t is 1 or 2), —$S(O)_tOR^a$ (where t is 1 or 2), —$S(O)_tN(R^a)_2$ (where t is 1 or 2), or —O—$P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein. The terms "alkenoxycarbonyl" and "alkynoxycarbonyl" mirror the above description of "alkoxycarbonyl" wherein the prefix "alk" is replaced with "alken" or "alkyn" respectively, and the parent "alkenyl" or "alkynyl" terms are as described herein.

"Acyl" refers to R—C(O)— groups such as, but not limited to, H, (alkyl)-C(O)—, (alkenyl)-C(O)—, (alkynyl)-C(O)—, (aryl)-C(O)—, (cycloalkyl)-C(O)—, (heteroaryl)-C(O)—, (heteroalkyl)-C(O)—, and (heterocycloalkyl)-C(O)—, wherein the group is attached to the parent molecular structure through the carbonyl functionality. In some embodiments, provided herein is a C_1-C_{10} acyl radical which refers to the total number of chain or ring atoms of the, for example, alkyl, alkenyl, alkynyl, aryl, cyclohexyl, heteroaryl or heterocycloalkyl portion plus the carbonyl carbon of acyl. For example, a C_4-acyl has three other ring or chain atoms plus carbonyl. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise in the specification, the "R" of an acyloxy group can be optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, —$Si(R^a)_3$, —OR^a, —SR^a, —$OC(O)—R^a$, —$N(R^a)_2$, —$C(O)R^a$, —$C(O)OR^a$, —$OC(O)N(R^a)_2$, —$C(O)N(R^a)_2$, —$N(R^a)C(O)OR^a$, —$N(R^a)C(O)R^a$, —$N(R^a)C(O)N(R^a)_2$, —$N(R^a)C(NR^a)N(R^a)_2$, —$N(R^a)S(O)_tR^a$ (where t is 1 or 2), —$S(O)_tOR^a$ (where t is 1 or 2), —$S(O)_tN(R^a)_2$ (where t is 1 or 2), or —O—$P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

"Acyloxy" refers to a R(C=O)O— radical wherein "R" can be H, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, cyclohexyl, heteroaryl, or heterocycloalkyl, which are as described herein. The acyloxy group is attached to the parent molecular structure through the oxygen functionality. In some embodiments, an acyloxy group is a C_1-C_4 acyloxy radical which refers to the total number of chain or ring atoms of the alkyl, alkenyl, alkynyl, aryl, cyclohexyl, heteroaryl or heterocycloalkyl portion of the acyloxy group plus the carbonyl carbon of acyl, e.g., a C_4-acyloxy has three other ring or chain atoms plus carbonyl. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise in the specification, the "R" of an acyloxy group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, —$Si(R^a)_3$, —OR^a, —SR^a, —$OC(O)—R^a$, —$N(R^a)_2$, —$C(O)R^a$, —$C(O)OR^a$, —$OC(O)N(R^a)_2$, —$C(O)N(R^a)_2$, —$N(R^a)C(O)OR^a$, —$N(R^a)C(O)R^a$, —$N(R^a)C(O)N(R^a)_2$, —$N(R^a)C(NR^a)N(R^a)_2$, —$N(R^a)S(O)_tR^a$ (where t is 1 or 2), —$S(O)_tOR^a$ (where t is 1 or 2), —$S(O)_tN(R^a)_2$ (where t is 1 or 2), or —O—$P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

The terms "amine" and "amino" can also refer to N-oxides of the groups —$N^+(H)(R^a)O^-$, and —$N^+(R^a)(R^a)O^-$, where R^a is as described above, where the N-oxide is bonded to the parent molecular structure through the N atom. N-oxides can be prepared by treatment of the corresponding amino group with, for example, hydrogen peroxide or m-chloroperoxybenzoic acid. The person skilled in the art is familiar with reaction conditions for carrying out the N-oxidation.

"Amino" or "amine" refers to a —$N(R^b)_2$, —$N(R^b)R^b$—, or —$R^bN(R^b)R^b$— radical group, where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein. When a —$N(R^b)_2$ group has two R^b other than hydrogen, they can be combined with the nitrogen atom to form a 3-, 4-, 5-, 6-, 7-, or 8-membered ring. For example, —$N(R^b)_2$ is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. Unless stated otherwise in the specification, an amino group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfonyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, —$Si(R^a)_3$, —OR^a, —$OC(O)—R^a$, —$N(R^a)_2$, —$C(O)R^a$, —$C(O)OR^a$, —$OC(O)N(R^a)_2$, —$C(O)N(R^a)_2$, —$N(R^a)C(O)OR^a$, —$N(R^a)C(O)R^a$, —$N(R^a)C(O)N(R^a)_2$, —$N(R^a)C(NR^a)N(R^a)_2$, —$N(R^a)S(O)_tR^a$ (where t is 1 or 2), —$S(O)_tOR^a$ (where t is 1 or 2), —$S(O)_tN(R^a)_2$ (where t is 1 or 2), or —O—$P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

"Amide" or "amido" refers to a chemical moiety with formula —C(O)N(R^b)$_2$ or —NR^bC(O)R^b, where R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein. In some embodiments, an amido or amide radical is a C_1-C_4 amido or amide radical, which includes the amide carbonyl in the total number of carbons in the radical. When a —C(O)N(R^b)$_2$ has two R^b other than hydrogen, they can be combined with the nitrogen atom to form a 3-, 4-, 5-, 6-, 7-, or 8-membered ring. For example, N(R^b)$_2$ portion of a —C(O)N(R^b)$_2$ radical is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. Unless stated otherwise in the specification, an amido R^b group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, —Si(R^a)$_3$, —OR^a, —SR^a, —OC(O)—R^a, —N(R^a)$_2$, —C(O)R^a, —C(O)OR^a, —OC(O)N(R^a)$_2$, —C(O)N(R^a)$_2$, —N(R^a)C(O)OR^a, —N(R^a)C(O)R^a, N(R^a)C(O)N(R^a)$_2$, —N(R^a)C(NR^a)N(R^a)$_2$, —N(R^a)S(O)$_t$$R^a$ (where t is 1 or 2), —S(O)$_t$OR^a (where t is 1 or 2), —S(O)$_t$N(R^a)$_2$ (where t is 1 or 2), or —O—P(=O)(OR^a)$_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

The term "amide" or "amido" is inclusive of an amino acid or a peptide molecule. Any amine, hydroxy, or carboxyl side chain on the compounds described herein can be transformed into an amide group. The procedures and specific groups to make such amides are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, *Protective Groups in Organic Synthesis,* 4th Ed., John Wiley & Sons, New York, N.Y., 2006, which is incorporated herein by reference in its entirety.

"Amidino" refers to the —C(=NR^b)N(R^b)$_2$, —N(R^b)—C(=NR^b)—R^b, and —N(R^b)—C(=NR^b)— radicals, where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

"Aryl" refers to a radical with six to fourteen ring atoms (e.g., C_6-C_{14} or C_6-C_{10} aryl) which has at least one carbocyclic ring having a conjugated pi electron system which is aromatic (e.g., having 6, 10, or 14 π electrons shared in a cyclic array) (e.g., phenyl, fluorenyl, and naphthyl). In one embodiment, bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. In other embodiments, bivalent radicals derived from univalent monocyclic or polycyclic hydrocarbon radicals whose names end in "-yl" by removal of one hydrogen atom from the carbon atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, e.g., a naphthyl group with two points of attachment is termed naphthylidene. Whenever it appears herein, a numerical range such as "6 to 10 aryl" refers to each integer in the given range; e.g., "6 to 10 ring atoms" means that the aryl group can consist of 6 ring atoms, 7 ring atoms, etc., up to and including 10 ring atoms. The term includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of ring atoms) groups. Unless stated otherwise in the specification, an aryl moiety can be optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, —Si(R^a)$_3$, —OR^a, —SR^a, —OC(O)—R^a, —N(R^a)$_2$, —C(O)R^a, —C(O)OR^a, —OC(O)N(R^a)$_2$, —C(O)N(R^a)$_2$, —N(R^a)C(O)OR^a, —N(R^a)C(O)R^a, N(R^a)C(O)N(R^a)$_2$, —N(R^a)C(NR^a)N(R^a)$_2$, —N(R^a)S(O)$_t$$R^a$ (where t is 1 or 2), —S(O)$_t$OR^a (where t is 1 or 2), —S(O)$_t$N(R^a)$_2$ (where t is 1 or 2), or —O—P(=O)(OR^a)$_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein. In one embodiment, unless stated otherwise, "aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more cycloalkyl or heterocyclyl groups wherein the point of attachment to the parent molecular structure is on the aryl ring.

"Aralkyl" or "arylalkyl" refers to an (aryl)alkyl-radical where aryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively. The "aralkyl" or "arylalkyl" is bonded to the parent molecular structure through the alkyl group. The terms "aralkenyl/arylalkenyl" and "aralkynyl/arylalkynyl" mirror the above description of "aralkyl/arylalkyl" wherein the "alkyl" is replaced with "alkenyl" or "alkynyl" respectively, and the "alkenyl" or "alkynyl" terms are as described herein.

"Azide" refers to a —N_3 radical.

"Carbamate" refers to any of the following radicals: —O—(C=O)—N(R^b)—, —O—(C=O)—N(R^b)$_2$, —N(R^b)—(C=O)—O—, and —N(R^b)—(C=O)—OR^b, wherein each R^b is independently selected from H, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

"Carbonate" refers to a —O—(C=O)—O— or —O—(C=O)—OR radical, where R can be hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, cyclohexyl, heteroaryl, or heterocycloalkyl, which are as described herein.

"Carbonyl" refers to a —(C=O)— radical.

"Carboxaldehyde" refers to a —(C=O)H radical.

"Carboxyl" refers to a —(C=O)OH radical.

"Cyano" refers to a —CN radical.

"Cycloalkyl," or alternatively, "carbocyclyl," refers to a monocyclic or polycyclic radical that contains only carbon and hydrogen, and can be saturated or partially unsaturated. Partially unsaturated cycloalkyl groups can be termed

"cycloalkenyl" if the carbocycle contains at least one double bond, or "cycloalkynyl" if the carbocycle contains at least one triple bond. Cycloalkyl groups include groups having from 3 to 10 ring atoms (e.g., C_3-C_{10} cycloalkyl). Whenever it appears herein, a numerical range such as "3 to 10" refers to each integer in the given range; e.g., "3 to 10 carbon atoms" means that the cycloalkyl group can consist of 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, etc., up to and including 10 carbon atoms. The term "cycloalkyl" also includes bridged and spiro-fused cyclic structures containing no heteroatoms. The term also includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of ring atoms) groups. In some embodiments, it is a C_3-C_8 cycloalkyl radical. In some embodiments, it is a C_3-C_5 cycloalkyl radical. Illustrative examples of cycloalkyl groups include, but are not limited to the following moieties: C_{3-6} carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclobutyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Examples of C_{3-8} carbocyclyl groups include the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, and the like. Examples of C_{3-10} carbocyclyl groups include the aforementioned C_{3-8} carbocyclyl groups as well as octahydro-1H-indenyl, decahydronaphthalenyl, spiro[4.5]decanyl, and the like. Unless stated otherwise in the specification, a cycloalkyl group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfonyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, —$Si(R^a)_3$, —OR^a, —SR^a, —OC(O)—R^a, —$N(R^a)_2$, —$C(O)R^a$, —$C(O)OR^a$, —$OC(O)N(R^a)_2$, —$C(O)N(R^a)_2$, —$N(R^a)C(O)OR^a$, —$N(R^a)C(O)R^a$, —$N(R^a)C(O)N(R^a)_2$, —$N(R^a)C(NR^a)N(R^a)_2$, —$N(R^a)S(O)_tR^a$ (where t is 1 or 2), —$S(O)_tOR^a$ (where t is 1 or 2), —$S(O)_tN(R^a)_2$ (where t is 1 or 2), or —O—$P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein. In one embodiment, unless stated otherwise, "cycloalkyl" or "carbocyclyl" also includes ring systems wherein the cycloalkyl or carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment to the parent molecular structure is on the cycloalkyl or carbocyclyl ring.

"Cycloalkyl-alkyl" refers to a -(cycloalkyl)alkyl radical where cycloalkyl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and alkyl respectively. The "cycloalkyl-alkyl" is bonded to the parent molecular structure through the cycloalkyl group. The terms "cycloalkyl-alkenyl" and "cycloalkyl-alkynyl" mirror the above description of "cycloalkyl-alkyl" wherein the term "alkyl" is replaced with "alkenyl" or "alkynyl" respectively, and "alkenyl" or "alkynyl" are as described herein.

"Cycloalkyl-heterocycloalkyl" refers to a -(cycloalkyl) heterocyclylalkyl radical where cycloalkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocycloalkyl and cycloalkyl respectively. The "cycloalkyl-heterocycloalkyl" is bonded to the parent molecular structure through the cycloalkyl group.

"Cycloalkyl-heteroaryl" refers to a -(cycloalkyl)heteroaryl radical where cycloalkyl and heteroaryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroaryl and cycloalkyl respectively. The "cycloalkyl-heteroaryl" is bonded to the parent molecular structure through the cycloalkyl group.

As used herein, a "covalent bond" or "direct bond" refers to a single bond joining two groups.

"Ester" refers to a radical of formula —COOR, where R is selected from alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl. Any amine, hydroxy, or carboxyl side chain on the compounds described herein can be esterified. The procedures and specific groups to make such esters are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, *Protective Groups in Organic Synthesis*, 4th Ed., John Wiley & Sons, New York, N.Y., 2006, which is incorporated herein by reference in its entirety. Unless stated otherwise in the specification, an ester group can be optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, —$Si(R^a)_3$, OR^a, —SR^a, —OC(O)—R^a, —$N(R^a)_2$, —$C(O)R^a$, —$C(O)OR^a$, —$OC(O)N(R^a)_2$, —$C(O)N(R^a)_2$, —$N(R^a)C(O)OR^a$, —$N(R^a)C(O)R^a$, $N(R^a)C(O)N(R^a)_2$, —$N(R^a)C(NR^a)N(R^a)_2$, —$N(R^a)S(O)_tR^a$ (where t is 1 or 2), —$S(O)_tOR^a$ (where t is 1 or 2), —$S(O)_tN(R^a)_2$ (where t is 1 or 2), or —O—$P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

"Ether" refers to a —R^b—O—R^b radical where each R^b is independently selected from alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

"Halo", "halide", or, alternatively, "halogen" means fluoro, chloro, bromo, or iodo. The terms "haloalkyl," "haloalkenyl," "haloalkynyl" and "haloalkoxy" include alkyl, alkenyl, alkynyl and alkoxy structures that are substituted with one or more halo groups or with combinations thereof. For example, the terms "fluoroalkyl" and "fluoroalkoxy" include haloalkyl and haloalkoxy groups, respectively, in which the halo is fluorine, such as, but not limited to, trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. Each of the alkyl, alkenyl, alkynyl and alkoxy groups are as defined herein and can be optionally further substituted as defined herein.

"Heteroalkyl", "heteroalkenyl" and "heteroalkynyl" include alkyl, alkenyl and alkynyl radicals, respectively, which have one or more skeletal chain atoms selected from an

atom other than carbon, e.g., oxygen, nitrogen, sulfur, and phosphorus, or combinations thereof. A numerical range can be given, e.g., C_1-C_4 heteroalkyl which refers to the chain length in total, which in this example can be up to 4 atoms long. For example, a $—CH_2OCH_2CH_3$ radical is referred to as a "C_4" heteroalkyl, which includes the heteroatom center in the atom chain length description. Connection to the parent molecular structure can be through either a heteroatom or a carbon in the heteroalkyl chain. For example, an N-containing heteroalkyl moiety refers to a group in which at least one of the skeletal atoms is a nitrogen atom. One or more heteroatom(s) in the heteroalkyl radical can be optionally oxidized. One or more nitrogen atoms, if present, can also be optionally quaternized. For example, heteroalkyl also includes skeletal chains substituted with one or more nitrogen oxide (—O—) substituents. Exemplary heteroalkyl groups include, without limitation, ethers such as methoxyethanyl ($—CH_2CH_2OCH_3$), ethoxymethanyl ($—CH_2OCH_2CH_3$), (methoxymethoxy)ethanyl ($—CH_2CH_2—OCH_2OCH_3$), (methoxymethoxy)methanyl ($—CH_2OCH_2OCH_3$), and (methoxyethoxy)methanyl ($—CH_2OCH_2CH_2OCH_3$), and the like; amines such as $—CH_2CH_2NHCH_3$, $—CH_2CH_2N(CH_3)_2$, $—CH_2NHCH_2CH_3$, $—CH_2N(CH_2CH_3)(CH_3)$, and the like. Heteroalkyl, heteroalkenyl, and heteroalkynyl groups can each be optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $—Si(R^a)_3$, $—OR^a$, $—SR^a$, $—OC(O)—R^a$, $—N(R^a)_2$, $—C(O)R^a$, $—C(O)OR^a$, $—OC(O)N(R^a)_2$, $—C(O)N(R^a)_2$, $—N(R^a)C(O)OR^a$, $—N(R^a)C(O)R^a$, $N(R^a)C(O)N(R^a)_2$, $—N(R^a)C(NR^a)N(R^a)_2$, $—N(R^a)S(O)_tR^a$ (where t is 1 or 2), $—S(O)_tOR^a$ (where t is 1 or 2), $—S(O)_tN(R^a)_2$ (where t is 1 or 2), or $—O—P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

"Heteroalkyl-aryl" refers to a -(heteroalkyl)aryl radical where heteroalkyl and aryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and aryl respectively. The "heteroalkyl-aryl" is bonded to the parent molecular structure through an atom of the heteroalkyl group.

"Heteroalkyl-heteroaryl" refers to a -(heteroalkyl)heteroaryl radical where heteroalkyl and heteroaryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and heteroaryl respectively. The "heteroalkyl-heteroaryl" is bonded to the parent molecular structure through an atom of the heteroalkyl group.

"Heteroalkyl-heterocycloalkyl" refers to a -(heteroalkyl) heterocycloalkyl radical where heteroalkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and heterocycloalkyl respectively. The "heteroalkyl-heterocycloalkyl" is bonded to the parent molecular structure through an atom of the heteroalkyl group.

"Heteroalkyl-cycloalkyl" refers to a -(heteroalkyl)cycloalkyl radical where heteroalkyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and cycloalkyl respectively. The "heteroalkyl-cycloalkyl" is bonded to the parent molecular structure through an atom of the heteroalkyl group.

"Heteroaryl", or alternatively, "heteroaromatic", refers to a radical of a 5- to 18-membered monocyclic or polycyclic (e.g., bicyclic or tricyclic) aromatic ring system (e.g., having 6, 10 or 14 electrons shared in a cyclic array) having ring carbon atoms and 1 to 6 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5- to 18-membered heteroaryl"). Heteroaryl polycyclic ring systems can include one or more heteroatoms in one or more rings. Whenever it appears herein, a numerical range such as "5 to 18" refers to each integer in the given range; e.g., "5 to 18 ring atoms" means that the heteroaryl group can consist of 5 ring atoms, 6 ring atoms, 7 ring atoms, 8 ring atoms, 9 ring atoms, 10 ring atoms, etc., up to and including 18 ring atoms. In one embodiment, bivalent radicals derived from univalent heteroaryl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, e.g., a pyridyl group with two points of attachment is a pyridylidene.

For example, an N-containing "heteroaromatic" or "heteroaryl" moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. One or more heteroatom(s) in the heteroaryl radical can be optionally oxidized. One or more nitrogen atoms, if present, can also be optionally quaternized. Heteroaryl also includes ring systems substituted with one or more nitrogen oxide (—O—) substituents, such as pyridinyl N-oxides. The heteroaryl is attached to the parent molecular structure through any atom of the ring(s).

"Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment to the parent molecular structure is either on the aryl or on the heteroaryl ring, or wherein the heteroaryl ring, as defined above, is fused with one or more cycloalkyl or heterocyclyl groups wherein the point of attachment to the parent molecular structure is on the heteroaryl ring. For polycyclic heteroaryl groups wherein one ring does not contain a heteroatom (e.g., indolyl, quinolinyl, carbazolyl and the like), the point of attachment to the parent molecular structure can be on either the ring bearing a heteroatom (e.g., 2-indolyl) or the ring that does not contain a heteroatom (e.g., 5-indolyl). In some embodiments, a heteroaryl group is a 5 to 10 membered aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5- to 10-membered heteroaryl"). In some embodiments, a heteroaryl group is a 5- to 8-membered aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5- to 8-membered heteroaryl"). In some embodiments, a heteroaryl group is a 5- to 6-membered aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5- to 6-membered heteroaryl"). In some embodiments, the 5- to 6-membered heteroaryl has 1 to 3 ring heteroatoms independently selected from nitrogen, oxygen, phosphorous, and sulfur. In some embodiments, the 5- to 6-membered heteroaryl has 1 to 2 ring heteroatoms independently selected from

nitrogen, oxygen, phosphorous, and sulfur. In some embodiments, the 5- to 6-membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, phosphorous, and sulfur.

Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzofurazanyl, benzothiazolyl, benzothienyl (benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolinyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furazanyl, furanonyl, furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, thiapyranyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno[2,3-c]pridinyl, and thiophenyl (i.e., thienyl).

Unless stated otherwise in the specification, a heteroaryl moiety is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, —$Si(R^a)_3$, —OR^a, —SR^a, —$OC(O)—R^a$, —$N(R^a)_2$, —$C(O)R^a$, —$C(O)OR^a$, —$OC(O)N(R^a)_2$, —$C(O)N(R^a)_2$, —$N(R^a)C(O)OR^a$, —$N(R^a)C(O)R^a$, —$N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, —$N(R^a)S(O)_tR^a$ (where t is 1 or 2), —$S(O)_tOR^a$ (where t is 1 or 2), —$S(O)_tN(R^a)_2$ (where t is 1 or 2), or —$O—P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

"Heteroaryl-alkyl" refers to a -(heteroaryl)alkyl radical where heteroaryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroaryl and alkyl respectively. The "heteroaryl-alkyl" is bonded to the parent molecular structure through any atom of the heteroaryl group.

"Heteroaryl-heterocycloalkyl" refers to an -(heteroaryl) heterocycloalkyl radical where heteroaryl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroaryl and heterocycloalkyl respectively. The "heteroaryl-heterocycloalkyl" is bonded to the parent molecular structure through an atom of the heteroaryl group.

"Heteroaryl-cycloalkyl" refers to an -(heteroaryl)cycloalkyl radical where heteroaryl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroaryl and cycloalkyl respectively. The "heteroaryl-cycloalkyl" is bonded to the parent molecular structure through a carbon atom of the heteroaryl group.

"Heterocyclyl", "heterocycloalkyl" or 'heterocarbocyclyl" each refer to any 3- to 18-membered non-aromatic radical monocyclic or polycyclic moiety comprising at least one ring heteroatom selected from nitrogen, oxygen, phosphorous, and sulfur. A heterocyclyl group can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, wherein the polycyclic ring systems can be a fused, bridged or spiro ring system. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or more rings. A heterocyclyl group can be saturated or partially unsaturated. Partially unsaturated heterocycloalkyl groups can be termed "heterocycloalkenyl" if the heterocyclyl contains at least one double bond, or "heterocycloalkynyl" if the heterocyclyl contains at least one triple bond. Whenever it appears herein, a numerical range such as "5 to 18" refers to each integer in the given range; e.g., "5 to 18 ring atoms" means that the heterocyclyl group can consist of 5 ring atoms, 6 ring atoms, 7 ring atoms, 8 ring atoms, 9 ring atoms, 10 ring atoms, etc., up to and including 18 ring atoms. In one embodiment, bivalent radicals derived from univalent heterocyclyl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, e.g., a piperidyl group with two points of attachment is a piperidylidene.

An N-containing heterocyclyl moiety refers to an non-aromatic group in which at least one of the ring atoms is a nitrogen atom. The heteroatom(s) in the heterocyclyl radical can be optionally oxidized. One or more nitrogen atoms, if present, can be optionally quaternized. Heterocyclyl also includes ring systems substituted with one or more nitrogen oxide (—O—) substituents, such as piperidinyl N-oxides. The heterocyclyl is attached to the parent molecular structure through any atom of any of the ring(s).

"Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment to the parent molecular structure is on the heterocyclyl ring. In some embodiments, a heterocyclyl group is a 3- to 10-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("3- to 10-membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5- to 8-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5- to 8-membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5- to 6-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is indepen-

dently selected from nitrogen, oxygen, phosphorous, and sulfur ("5- to 6-membered heterocyclyl"). In some embodiments, the 5- to 6-membered heterocyclyl has 1 to 3 ring heteroatoms independently selected from nitrogen, oxygen, phosphorous, and sulfur. In some embodiments, the 5- to 6-membered heterocyclyl has 1 to 2 ring heteroatoms independently selected from nitrogen, oxygen, phosphorous, and sulfur. In some embodiments, the 5- to 6-membered heterocyclyl has 1 ring heteroatom selected from nitrogen, oxygen, phosphorous, and sulfur.

Exemplary 3-membered heterocyclyls containing 1 heteroatom include, without limitation, azirdinyl, oxiranyl, thiorenyl. Exemplary 4-membered heterocyclyls containing 1 heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5-membered heterocyclyls containing 1 heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyls containing 2 heteroatoms include, without limitation, dioxolanyl, oxathiolanyl and dithiolanyl. Exemplary 5-membered heterocyclyls containing 3 heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing 1 heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing 2 heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, dioxanyl, and triazinanyl. Exemplary 7-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary bicyclic heterocyclyl groups include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, tetrahydroindolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, decahydroisoquinolinyl, octahydrochromenyl, octahydroisochromenyl, decahydronaphthyridinyl, decahydro-1,8-naphthyridinyl, octahydropyrrolo[3,2-b]pyrrole, indolinyl, phthalimidyl, naphthalimidyl, chromanyl, chromenyl, 1H-benzo[e][1,4]diazepinyl, 1,4,5,7-tetrahydropyrano[3,4-b]pyrrolyl, 5,6-dihydro-4H-furo[3,2-b]pyrrolyl, 6,7-dihydro-5H-furo[3,2-b]pyranyl, 5,7-dihydro-4H-thieno[2,3-c]pyranyl, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridinyl, 2,3-dihydrofuro[2,3-b]pyridinyl, 4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridinyl, 4,5,6,7-tetrahydrofuro[3,2-c]pyridinyl, 4,5,6,7-tetrahydrothieno[3,2-b]pyridinyl, 1,2,3,4-tetrahydro-1,6-naphthyridinyl, and the like.

Unless stated otherwise, heterocyclyl moieties are optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $—Si(R^a)_3$, $—OR^a$, $—SR^a$, $—OC(O)—R^a$, $—N(R^a)_2$, $—C(O)R^a$, $—C(O)OR^a$, $—OC(O)N(R^a)_2$, $—C(O)N(R^a)_2$, $N(R^a)C(O)OR^a$, $—N(R^a)C(O)R^a$, $—N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $—N(R^a)S(O)_tR^a$ (where t is 1 or 2), $—S(O)_tOR^a$ (where t is 1 or 2), $—S(O)_tN(R^a)_2$ (where t is 1 or 2), or $—O—P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

"Heterocyclyl-alkyl" refers to a -(heterocyclyl)alkyl radical where heterocyclyl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocyclyl and alkyl respectively. The "heterocyclyl-alkyl" is bonded to the parent molecular structure through any atom of the heterocyclyl group. The terms "heterocyclyl-alkenyl" and "heterocyclyl-alkynyl" mirror the above description of "heterocyclyl-alkyl" wherein the term "alkyl" is replaced with "alkenyl" or "alkynyl" respectively, and "alkenyl" or "alkynyl" are as described herein.

"Imino" refers to the "$—C(=N—R^b)—R^b$" radical where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

"Moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

"Nitro" refers to the $—NO_2$ radical.

"Oxa" refers to the —O— radical.

"Oxo" refers to the =O radical.

"Phosphate" refers to a $—O—P(=O)(OR^b)_2$ radical, where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein. In some embodiments, when R^a is hydrogen and depending on the pH, the hydrogen can be replaced by an appropriately charged counter ion.

"Phosphonate" refers to a $—O—P(=O)(R^b)(OR^b)$ radical, where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon) and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein. In some embodiments, when R^a is hydrogen and depending on the pH, the hydrogen can be replaced by an appropriately charged counter ion.

"Phosphinate" refers to a $—P(=O)(R^b)(OR^b)$ radical, where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein. In some embodiments, when R^a is hydrogen and depending on the pH, the hydrogen can be replaced by an appropriately charged counter ion.

A "leaving group or atom" is any group or atom that will, under the reaction conditions, cleave from the starting material, thus promoting reaction at a specified site. Suitable non-limiting examples of such groups, unless otherwise specified, include halogen atoms, mesyloxy, p-nitrobenzensulphonyloxy, trifluoromethyloxy, and tosyloxy groups.

"Protecting group" has the meaning conventionally associated with it in organic synthesis, e.g., a group that selectively blocks one or more reactive sites in a multifunctional compound such that a chemical reaction can be carried out selectively on another unprotected reactive site and such that the group can readily be removed after the selective reaction is complete. A variety of protecting groups are disclosed, for example, in T. H. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Fourth Edition, John Wiley & Sons, New York (2006), incorporated herein by reference in its entirety. For example, a hydroxy protected form is where at least one of the hydroxy groups present in a compound is protected with a hydroxy protecting group. Likewise, amines and other reactive groups can similarly be protected.

As used herein, the terms "substituted" or "substitution" mean that at least one hydrogen present on a group atom (e.g., a carbon or nitrogen atom) is replaced with a permissible substituent, e.g., a substituent which upon substitution for the hydrogen results in a stable compound, e.g., a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group can have a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. Substituents can include one or more group(s) individually and independently selected from acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, azide, carbonate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfonyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $—Si(R^a)_3$, $—OR^a$, $—SR^a$, $—OC(O)—R^a$, $—N(R^a)_2$, $—C(O)R^a$, $—C(O)OR^a$, $—OC(O)N(R^a)_2$, $—C(O)N(R^a)_2$, $N(R^a)C(O)OR^a$, $—N(R^a)C(O)R^a$, $—N(R^a)C(O)N(R^a)_2$, $—N(R^a)C(NR^a)N(R^a)_2$, $—N(R^a)S(O)_t R^a$ (where t is 1 or 2), $—S(O)_tOR^a$ (where t is 1 or 2), $—S(O)_tN(R^a)_2$ (where t is 1 or 2), and $—O—P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein. For example, a cycloalkyl substituent can have a halide substituted at one or more ring carbons, and the like. The protecting groups that can form the protective derivatives of the above substituents are known to those of skill in the art and can be found in references such as Greene and Wuts, above.

"Silyl" refers to a $—Si(R^b)_3$ radical where each R^b is independently selected from alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

"Sulfanyl", "sulfide", and "thio" each refer to the radical $—S—R^b$, wherein R^b is selected from alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein. For instance, an "alkylthio" refers to the "alkyl-S—" radical, and "arylthio" refers to the "aryl-S—" radical, each of which are bound to the parent molecular group through the S atom. The terms "sulfide", "thiol", "mercapto", and "mercaptan" can also each refer to the group $—R^bSH$.

"Sulfinyl" or "sulfoxide" refers to the $—S(O)—R^b$ radical, wherein for "sulfonyl", R^b is H, and for "sulfoxide", R^b is selected from alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

"Sulfonyl" or "sulfone" refers to the $—S(O_2)—R^b$ radical, wherein R^b is selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

"Sulfonamidyl" or "sulfonamido" refers to the following radicals: $—S(=O)_2—N(R^b)_2$, $—N(R^b)—S(=O)_2—R^b$, $—S(=O)_2—N(R^b)—$, or $—N(R^b)—S(=O)_2—$, where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein. The R^b groups in $—S(=O)_2—N(R^b)_2$ or $—N(R^b)—S(=O)_2—R^b$ can be taken together with the nitrogen to which they are attached to form a 4-, 5-, 6-, 7-, or 8-membered heterocyclyl ring. In some embodiments, the term designates a C_1-C_4 sulfonamido, wherein each R^b in the sulfonamido contains 1 carbon, 2 carbons, 3 carbons, or 4 carbons total.

"Sulfoxyl" refers to a $—S(=O)_2OH$ radical.

"Sulfonate" refers to a $—S(=O)_2—OR^b$ radical, wherein R^b is selected from alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

"Thiocarbonyl" refers to a —(C=S)— radical.

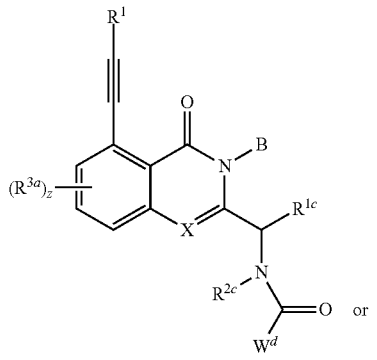
"Urea" refers to a $—N(R^b)—(C=O)—N(R^b)_2$ or $—N(R^b)—(C=O)—N(R^b)—$ radical, where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $—CH_2O—$ is equivalent to $—OCH_2—$.

Compounds

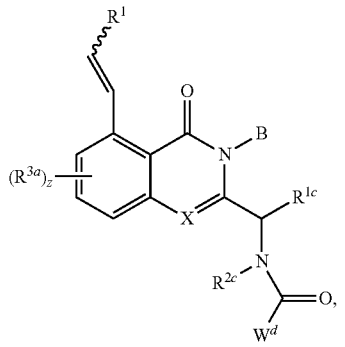
In certain embodiments, provided herein are compounds of Formula (I") or Formula (A"):

Formula (I")



or

Formula (A")



wherein:

R^1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, or —$CONR^4R^5$;

z is 0, 1, 2, or 3;

each instance of R^{3a} is independently hydrogen, alkyl, alkenyl, alkynyl, alkoxyl, halogen, cyano, amino, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

B is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, —$CONR^4R^5$, or —$Si(R^6)_3$;

wherein R^2, R^3, R^4, R^5, and R^6 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R^{1c} is hydrogen, alkyl, alkenyl, or alkynyl;

R^{2c} is hydrogen, alkyl, alkenyl, or alkynyl;

W^d is heteroaryl, cycloalkyl, heterocycloalkyl, or aryl; and

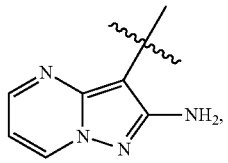
X is CR^{1a} or N;

wherein R^{1a} is hydrogen, halo, alkyl, alkenyl, alkynyl, or CN;

wherein each alkyl, alkenyl, or alkynyl is optionally substituted with one or more halo, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), $S(O)_2$(alkyl), cycloalkyl, heterocycloalkyl, aryl or heteroaryl;

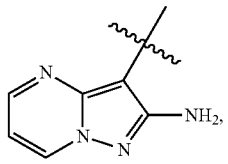
wherein each cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with one or more halo, alkyl, alkenyl, alkynyl, OH, alkoxy, oxo, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), or $S(O)_2$(alkyl);

wherein in Formula (I"), when X is CH, B is unsubstituted phenyl, and W^d is



then R^1 is not hydrogen, $Si(CH_3)_3$, $CH_2Si(CH_3)_3$, methyl, $(CH_2)NH_2$, $(CH_2)_2NH_2$, $(CH_2)NHSO_2CH_3$, or $(CH_2)_nNHC(O)R^{1x}$; n is 1 or 2; R^{1x} is methyl, C_2 alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl, where the alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl is optionally substituted with one or two groups independently selected from oxo and cyano;

wherein in Formula (A"), when X is CH, B is unsubstituted phenyl, and W^d is



then R^1 is not phenyl;

or a pharmaceutically acceptable form thereof.

In one embodiment, B is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, or —$CONR^4R^5$. In one embodiment, B is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, or —$CONR^4R^5$, wherein the point of attachment for the heterocycloalkyl and heteroaryl is a carbon atom.

In one embodiment, R^{1c} is alkyl, alkenyl, or alkynyl. In one embodiment, R^{1c} is hydrogen. In one embodiment, R^{1c} is alkyl. In one embodiment, R^{1c} is methyl or ethyl. In one embodiment, R^{1c} is methyl. In one embodiment, R^{1c} is ethyl.

In one embodiment, R^{2c} is hydrogen.

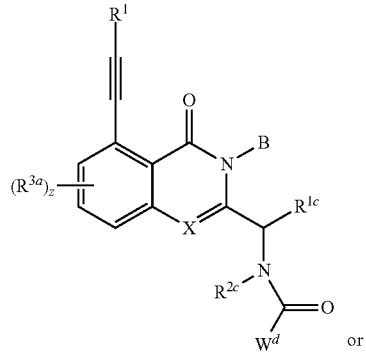
In one embodiment, in Formula (I"), X is N and $R^{2'}$ is hydrogen.

In one embodiment, z is 0. In another embodiment, z is 1. In another embodiment, z is 2. In another embodiment, z is 3.

In one embodiment, each instance of R^{3a} is independently hydrogen, alkyl, or halogen. In one embodiment, each instance of R^{3a} is independently hydrogen, methyl, fluoro, chloro, or bromo.

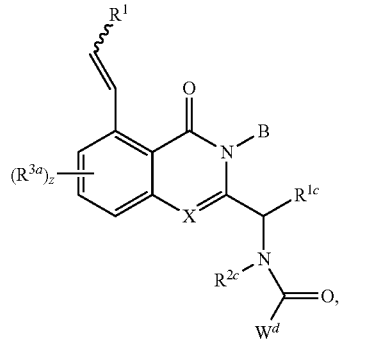
In certain embodiments, provided herein are compounds of Formula (I") or Formula (A"):

Formula (I")



or

Formula (A")



wherein:

R^1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, or —$CONR^4R^5$;

z is 0, 1, 2, or 3;

each instance of R^{3a} is independently hydrogen, alkyl, alkenyl, alkynyl, alkoxyl, halogen, cyano, amino, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

B is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, or —$CONR^4R^5$, wherein the point of attachment for the heterocycloalkyl and heteroaryl is a carbon atom;

wherein R^2, R^3, R^4, and R^5 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R^{1c} is alkyl, alkenyl, or alkynyl;

R^{2c} is hydrogen;

W^d is heteroaryl, cycloalkyl, heterocycloalkyl, or aryl; and

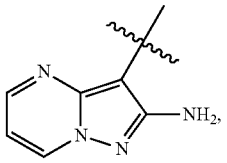
X is CR^{1a} or N;

wherein R^{1a} is hydrogen, halo, alkyl, alkenyl, alkynyl, or CN;

wherein each alkyl, alkenyl, or alkynyl is optionally substituted with one or more halo, OH, alkoxy, NH_2, NH(alkyl), N(alkyl)$_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), CON(alkyl)$_2$, S(O)(alkyl), S(O)$_2$(alkyl), cycloalkyl, heterocycloalkyl, aryl or heteroaryl;

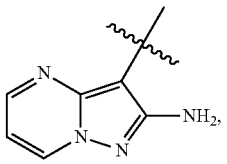
wherein each cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with one or more halo, alkyl, alkenyl, alkynyl, OH, alkoxy, oxo, NH_2, NH(alkyl), N(alkyl)$_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), CON(alkyl)$_2$, S(O)(alkyl), or S(O)$_2$(alkyl);

wherein in Formula (I"), when X is CH, B is unsubstituted phenyl, and W^d is



then R^1 is not hydrogen, $Si(CH_3)_3$, $CH_2Si(CH_3)_3$, methyl, $(CH_2)NH_2$, $(CH_2)_2NH_2$, $(CH_2)NHSO_2CH_3$, or $(CH_2)_nNHC(O)R^{1x}$; n is 1 or 2; R^{1x} is methyl, C_2 alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl, where the alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl is optionally substituted with one or two groups independently selected from oxo and cyano;

wherein in Formula (A"), when X is CH, B is unsubstituted phenyl, and W^d is

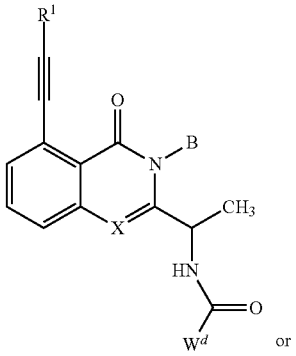


then R^1 is not phenyl;

or a pharmaceutically acceptable form thereof.

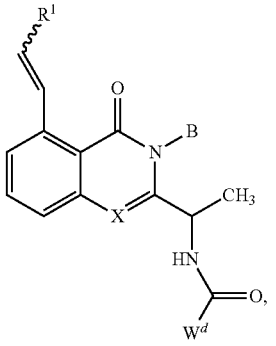
In certain embodiments, provided herein are compounds of Formula (I') or Formula (A'):

Formula (I')



or

Formula (A')



wherein:

R^1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, or —$CONR^4R^5$;

B is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, —$CONR^4R^5$, or —$Si(R^6)_3$;

wherein R^2, R^3, R^4, R^5, and R^6 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

W^d is heteroaryl, cycloalkyl, heterocycloalkyl, or aryl; and

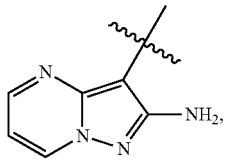
X is CR^{1a} or N;

wherein R^{1a} is hydrogen, halo, alkyl, alkenyl, alkynyl, or CN;

wherein each alkyl, alkenyl, or alkynyl is optionally substituted with one or more halo, haloalkyl, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), $S(O)_2$(alkyl), cycloalkyl, heterocycloalkyl, aryl or heteroaryl;

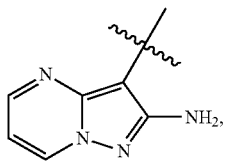
wherein each cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with one or more halo, haloalkyl, alkyl, alkenyl, alkynyl, OH, alkoxy, oxo, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), or $S(O)_2$(alkyl);

wherein in Formula (I"), when X is CH, B is unsubstituted phenyl, and W^d is



then R^1 is not hydrogen, $Si(CH_3)_3$, $CH_2Si(CH_3)_3$, methyl, $(CH_2)NH_2$, $(CH_2)_2NH_2$, $(CH_2)NHSO_2CH_3$, or $(CH_2)_nNHC(O)R^{1x}$; n is 1 or 2; R^{1x} is methyl, C_2 alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl, where the alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl is optionally substituted with one or two groups independently selected from oxo and cyano;

wherein in Formula (A"), when X is CH, B is unsubstituted phenyl, and W^d is

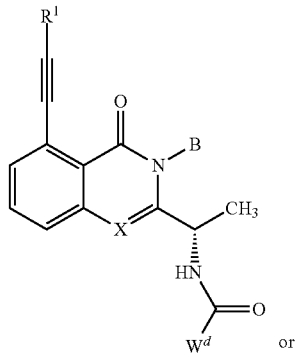


then R^1 is not phenyl;

or a pharmaceutically acceptable form thereof.

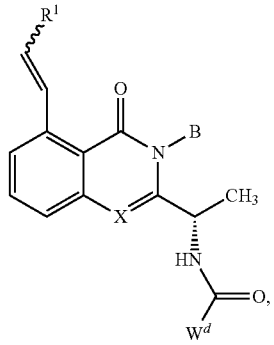
In certain embodiments, provided herein are compounds of Formula (I) or Formula (A):

Formula (I)



or

Formula (A)



wherein:

R^1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, or —$CONR^4R^5$;

B is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, —$CONR^4R^5$, or —$Si(R^6)_3$;

wherein R^2, R^3, R^4, R^5, and R^6 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

W^d is heteroaryl, cycloalkyl, heterocycloalkyl, or aryl; and

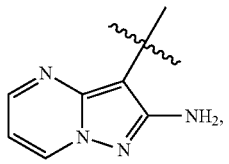
X is CR^{1a} or N;

wherein R^{1a} is hydrogen, halo, alkyl, alkenyl, alkynyl, or CN;

wherein each alkyl, alkenyl, or alkynyl is optionally substituted with one or more halo, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), $S(O)_2$(alkyl), cycloalkyl, heterocycloalkyl, aryl or heteroaryl;

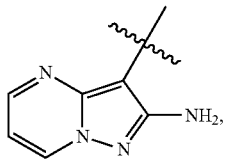
wherein each cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with one or more halo, alkyl, alkenyl, alkynyl, OH, alkoxy, oxo, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), or $S(O)_2$(alkyl);

wherein in Formula (I"), when X is CH, B is unsubstituted phenyl, and W^d is



then R^1 is not hydrogen, $Si(CH_3)_3$, $CH_2Si(CH_3)_3$, methyl, $(CH_2)NH_2$, $(CH_2)_2NH_2$, $(CH_2)NHSO_2CH_3$, or $(CH_2)_nNHC(O)R^{1x}$; n is 1 or 2; R^{1x} is methyl, C_2 alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl, where the alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl is optionally substituted with one or two groups independently selected from oxo and cyano;

wherein in Formula (A"), when X is CH, B is unsubstituted phenyl, and W^d is



then R^1 is not phenyl;

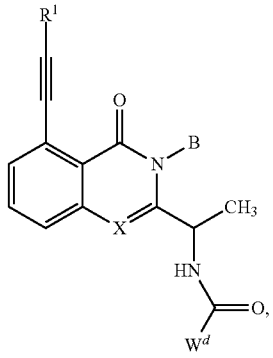
or a pharmaceutically acceptable form thereof.

In certain embodiments, provided herein is a mixture of compounds of Formula (I"), (I'), (I), (A"), (A'), or (A) wherein individual compounds of the mixture exist predominately in an (S)- or (R)-isomeric configuration. For example, the compound mixture has an (S)-enantiomeric purity of greater than about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, or more. In other embodiments, the compound mixture has an (S)-enantiomeric purity of greater than about 55% to about 99.5%, greater than about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99% to about 99.5%, or more.

In other embodiments, the compound mixture has an (R)-enantiomeric purity of greater than about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, or more. In some other embodiments, the compound mixture has an (R)-enantiomeric purity of greater than about 55% to about 99.5%, greater than about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5%, or more.

In certain embodiments, provided herein are compounds of Formula (I'):

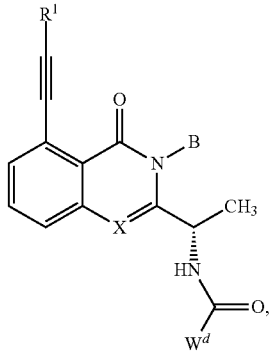
Formula (I')



or a pharmaceutically acceptable form thereof, wherein R^1, B, W^d and X are as defined herein.

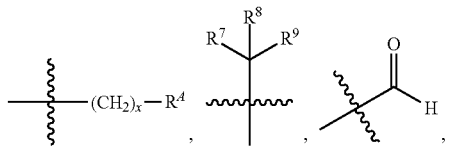
In certain embodiments, provided herein are compounds of Formula (I):

Formula (I)



or a pharmaceutically acceptable form thereof, wherein R^1, B, W^d and X are as defined herein.

In certain embodiments, R^1 is branched alkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, 5- or 6-membered cycloalkyl, or 5- or 6-membered heterocycloalkyl,



cyclopropyl, or methyl,

wherein R^A is OH, alkoxy, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

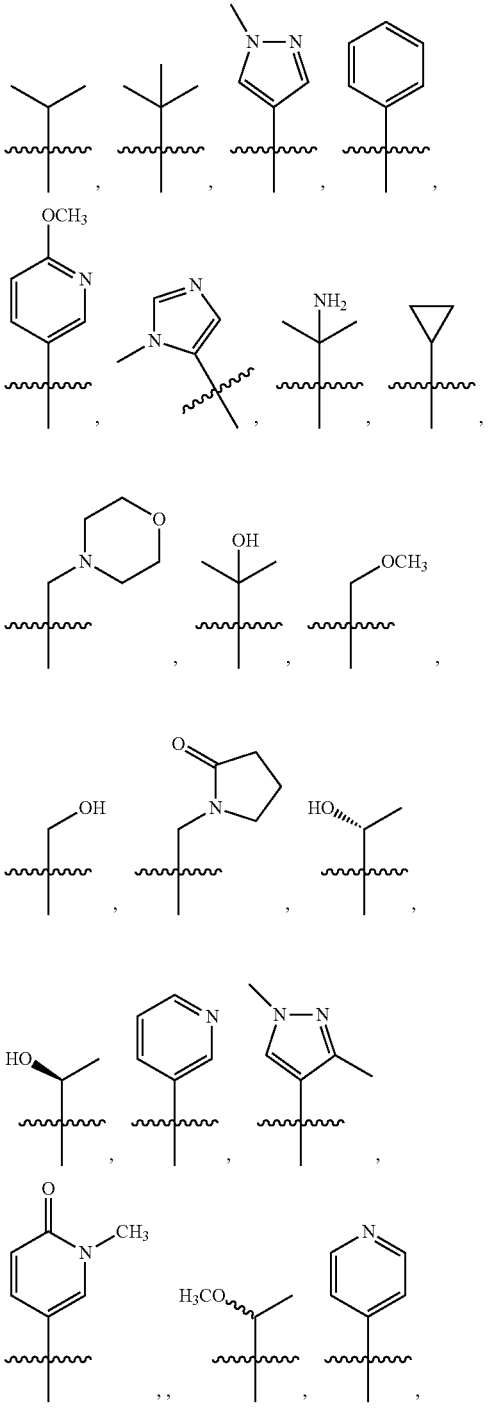
x is 1, 2, 3, 4, 5, or 6;

R^7, R^8, and R^9 are each, independently, hydrogen, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

In some embodiments, R^A is hydroxyl, alkoxy or heterocycloalkyl. In some embodiments, R^7, R^8, and R^9 are, independently, alkyl of 1-4 carbons, amino, hydroxyl, or alkoxy of 1-4 carbons.

In certain embodiments, R^1 is a 5- to 10-membered heteroaryl. In certain embodiments, R^1 is a 5- or 6-membered heteroaryl. In certain embodiments, R^1 is a 6-membered heteroaryl. In certain embodiments, R^1 is a pyridinyl. In certain embodiments, R^1 is a pyrimidinyl. In certain embodiments, R^1 is a 5-membered heteroaryl. In certain embodiments, R^1 is a thiazolyl. In certain embodiments, R^1 is a pyrazolyl. In certain embodiments, R^1 is an imidazolyl. In certain embodiments, the heteroaryl is substituted with one or more alkyl.

In some embodiments, R^1 is: methyl,



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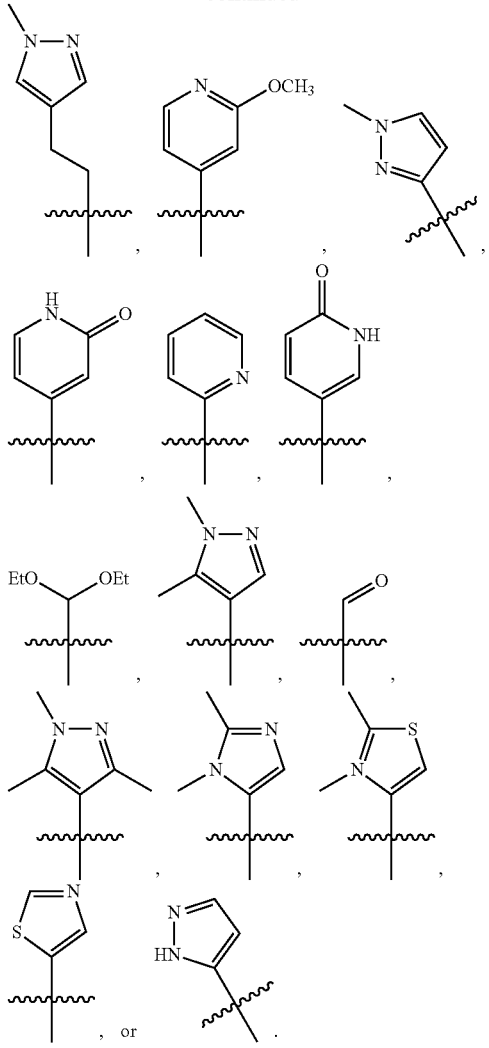
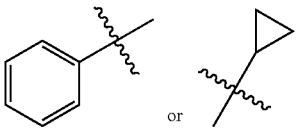
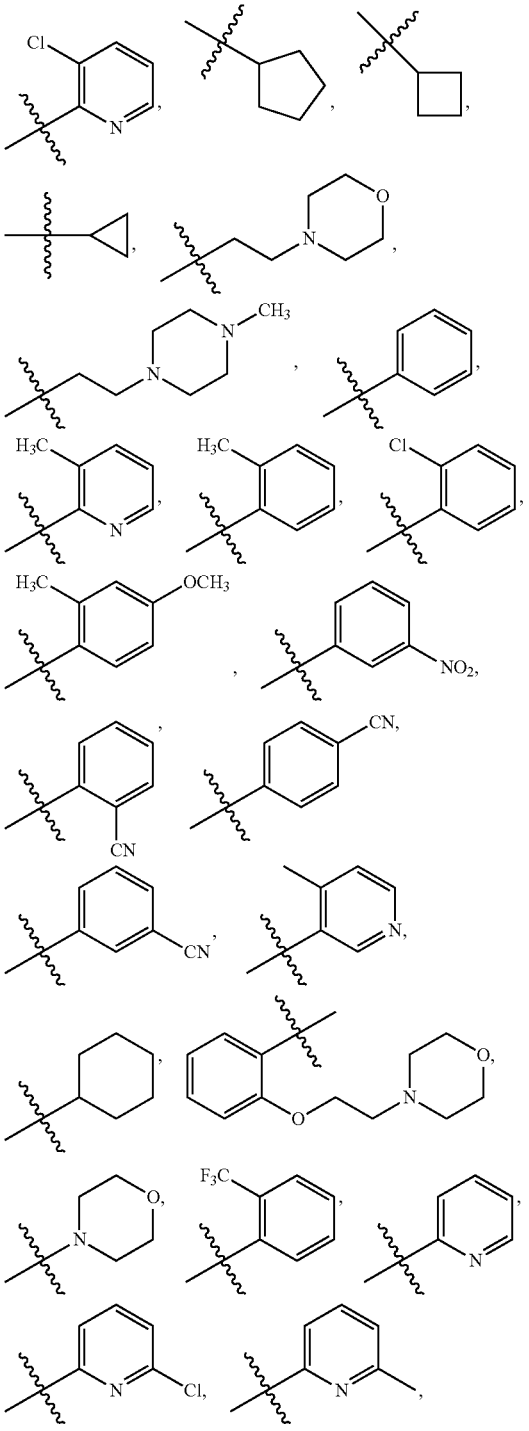


In some embodiments, B is phenyl substituted with 0, 1, 2, or 3 occurrence(s) of R^Z. In some embodiments, B is unsubstituted phenyl. In some embodiments, B is phenyl substituted with 1 or 2 occurrence(s) of R^Z. In some embodiments, B is phenyl optionally substituted at the para position with R^Z. In some embodiments, B is phenyl optionally mono-substituted at the meta position with R^Z. In some embodiments, B is phenyl optionally mono-substituted at the ortho position with R^Z. In some embodiments, B is phenyl optionally di-substituted at the meta positions with R^Z. In some embodiments, B is phenyl optionally di-substituted at the ortho positions with R^Z. In some embodiments, B is phenyl optionally di-substituted at the meta and ortho positions with R^Z. In some embodiments, B is phenyl optionally di-substituted at the meta and para positions with R^Z. In some embodiments, B is phenyl optionally di-substituted at the ortho and para positions with R^Z. In some embodiments, B is phenyl not substituted at the ortho positions. In some embodiments, R^Z is halo or alkyl. In some embodiments, B is methyl, isopropyl, or cyclopropyl. In some embodiments, B is cyclohexyl or optionally substituted alkyl. In some embodiments, B is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl. In some embodiments, B is 5- or 6-membered aryl or 3- to 6-membered cycloalkyl. In some embodiments, B is



In some embodiments, B is one of the following moieties: —CH_3, —CH_2CH_3, —$CH(CH_3)_2$,



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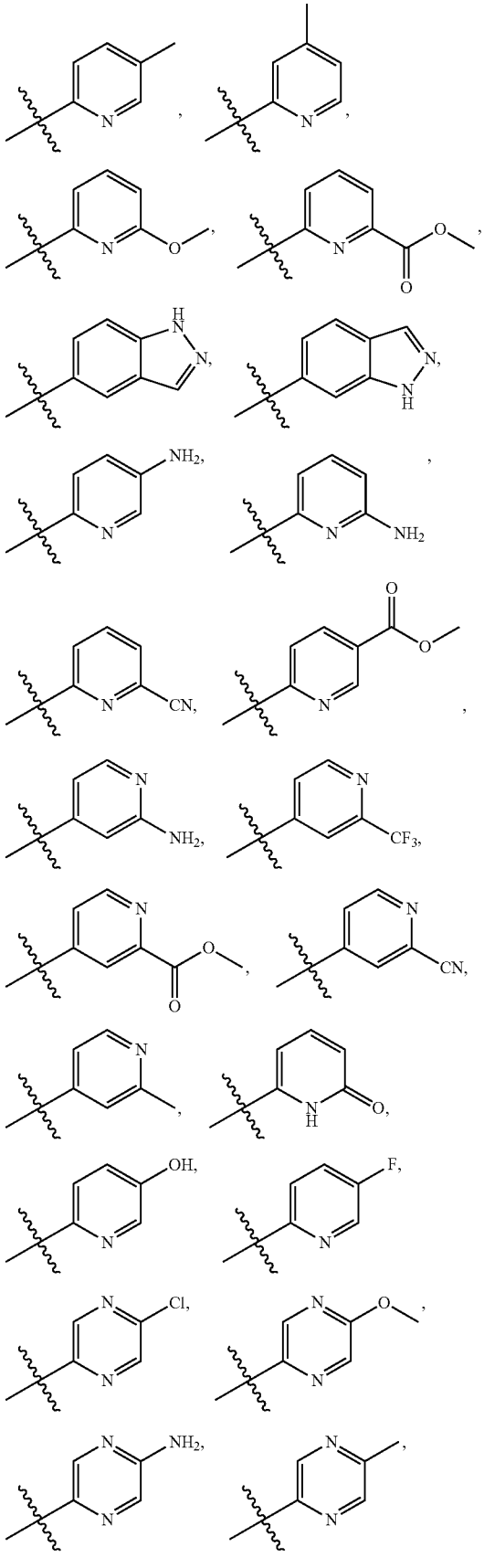

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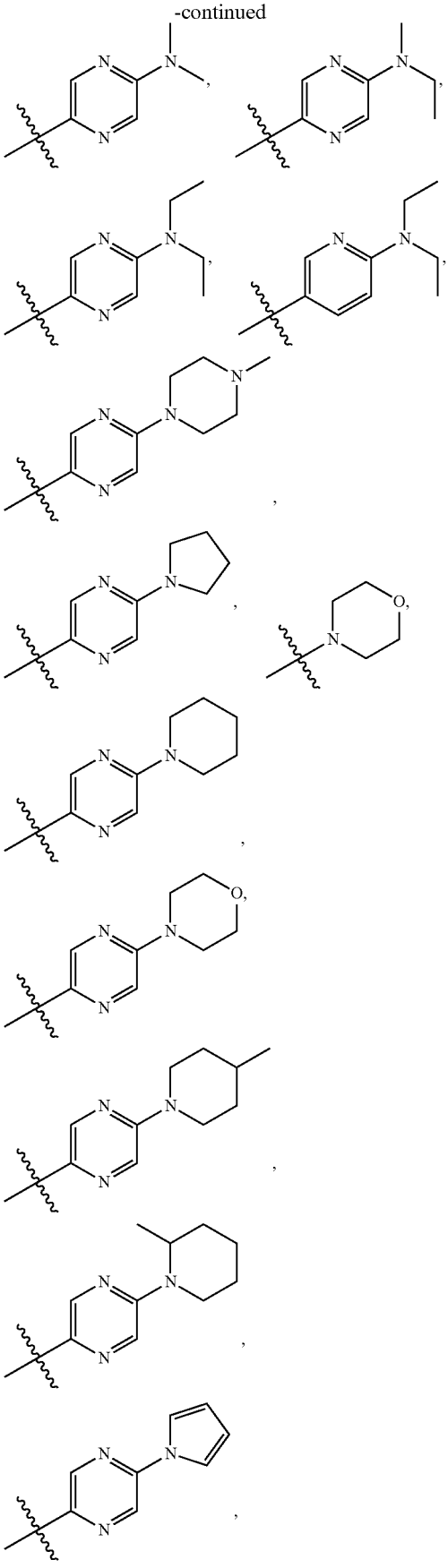

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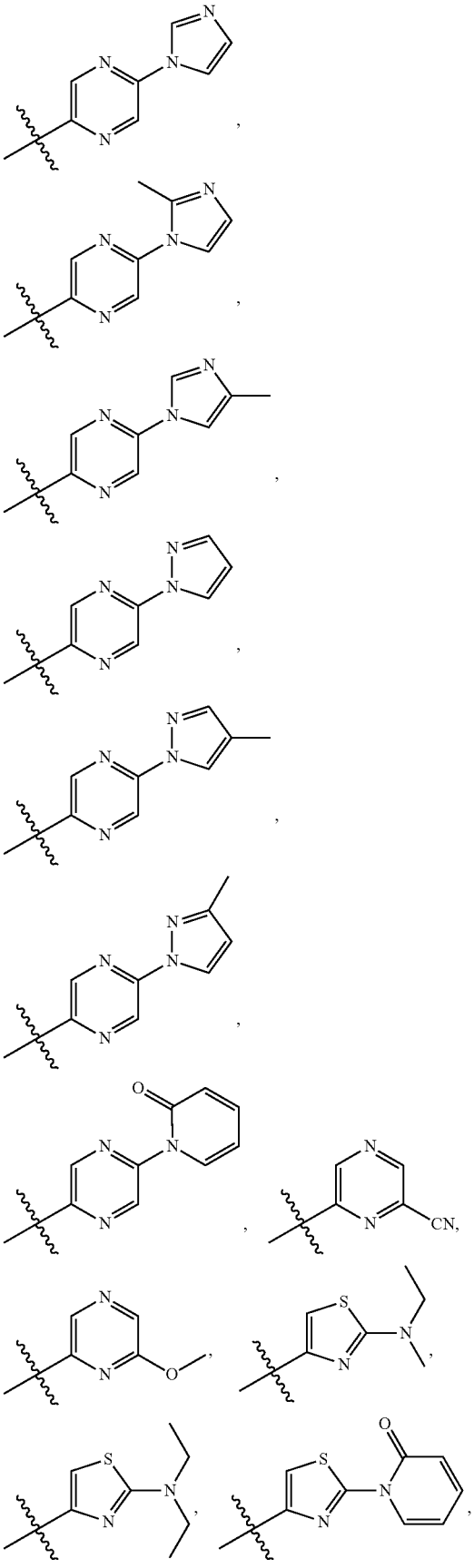

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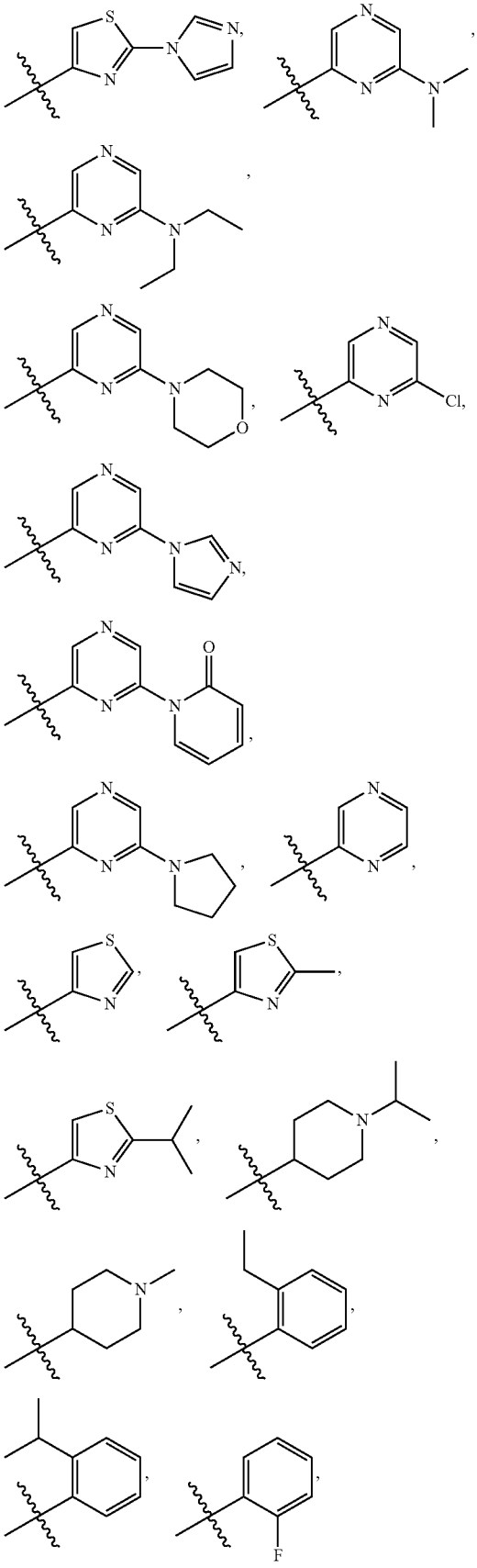

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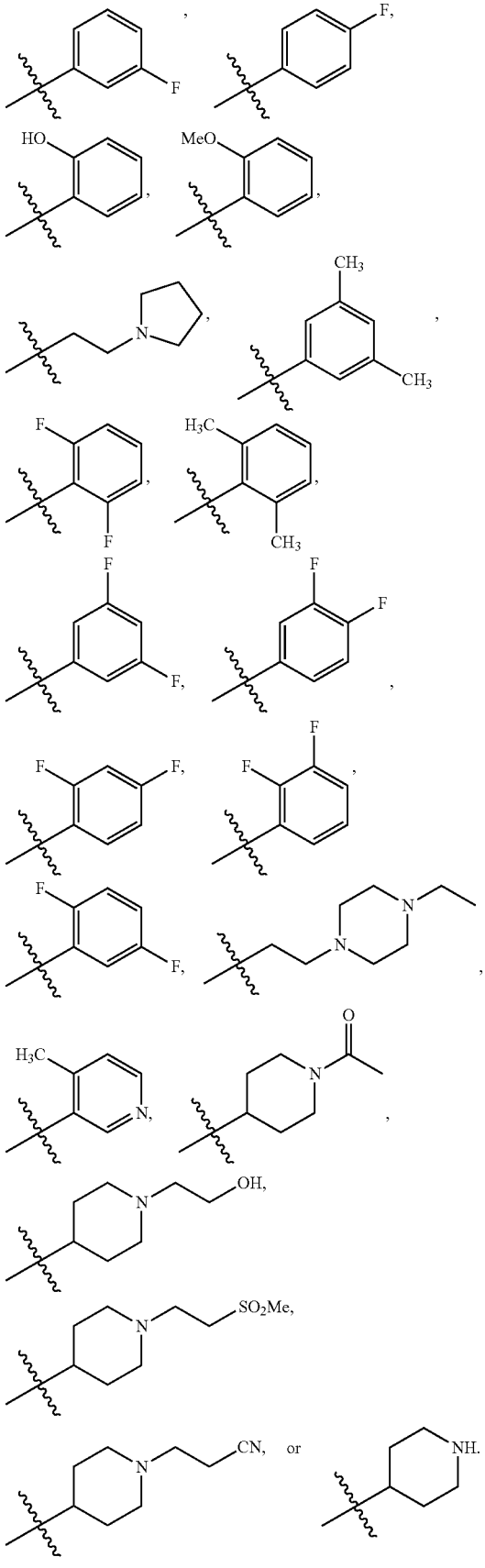


In some embodiments, B is selected from the moieties presented in Table 1.

TABLE 1

Illustrative B moieties of the compounds described herein.

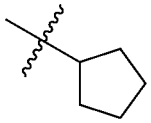
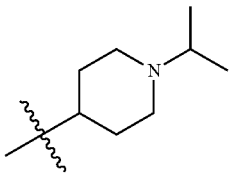
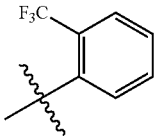
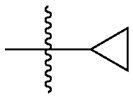
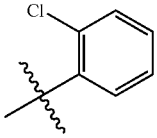
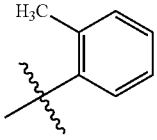
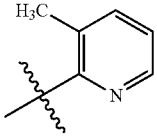
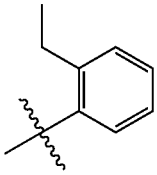
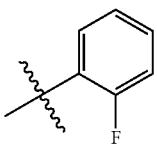
Sub-class #	B
B-1	
B-2	
B-3	—$CH(CH_3)_2$
B-4	
B-5	
B-6	
B-7	
B-8	
B-9	
B-10	

TABLE 1-continued

Illustrative B moieties of the compounds described herein.

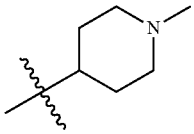
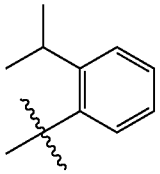
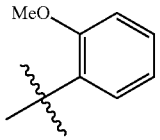
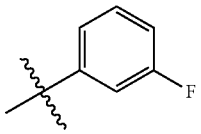
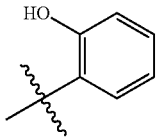
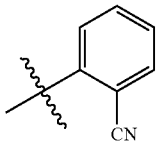
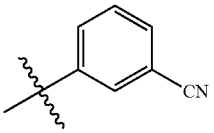
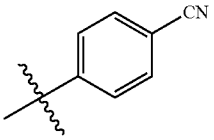
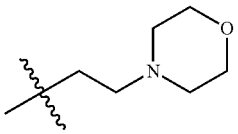
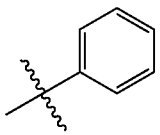
Sub-class #	B
B-11	
B-12	
B-13	
B-14	
B-15	
B-16	
B-17	
B-18	
B-19	
B-20	

TABLE 1-continued

Illustrative B moieties of the compounds described herein.

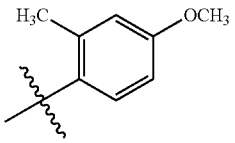
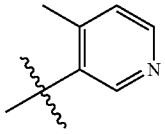
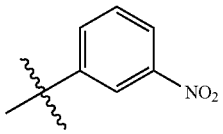
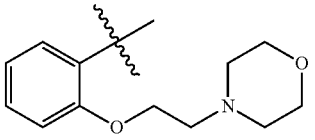
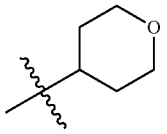
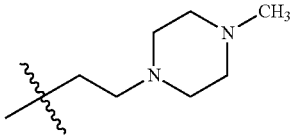
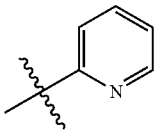
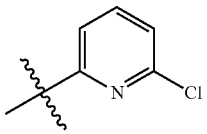
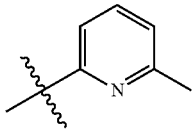
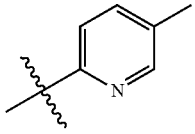
Sub-class #	B
B-21	
B-22	
B-23	
B-24	
B-25	
B-26	
B-27	
B-28	
B-29	
B-30	

TABLE 1-continued

Illustrative B moieties of the compounds described herein.

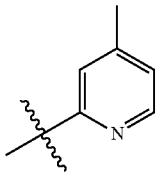
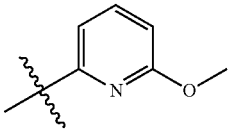
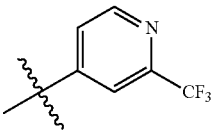
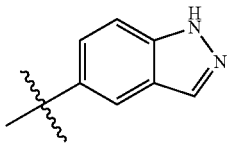
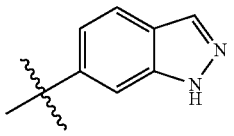
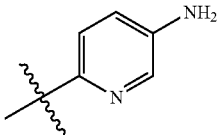
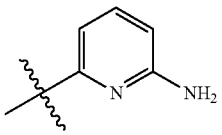
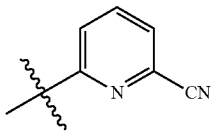
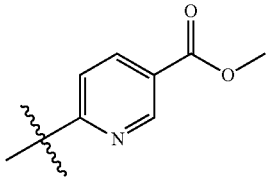
Sub-class #	B
B-31	
B-32	
B-33	
B-34	
B-35	
B-36	
B-37	
B-38	
B-39	

TABLE 1-continued

Illustrative B moieties of the compounds described herein.

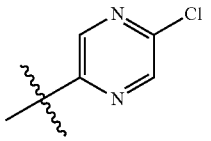
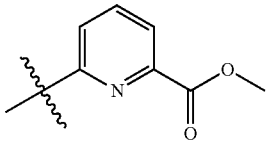
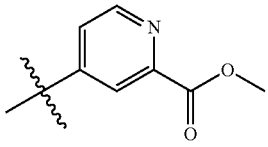
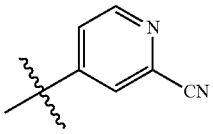
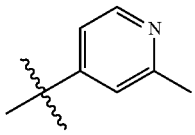
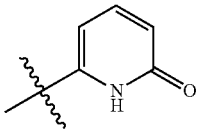
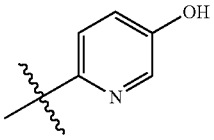
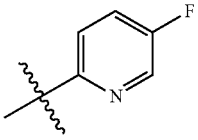
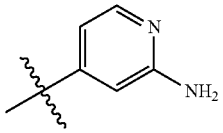
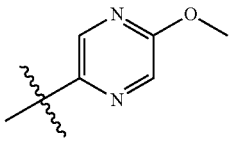
Sub-class #	B
B-40	
B-41	
B-42	
B-43	
B-44	
B-45	
B-46	
B-47	
B-48	
B-49	

TABLE 1-continued

Illustrative B moieties of the compounds described herein.

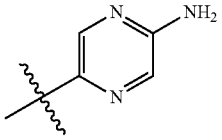
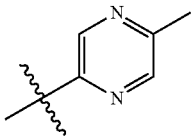
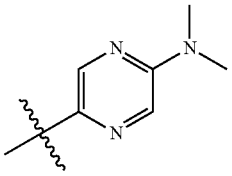
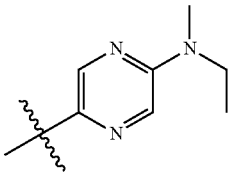
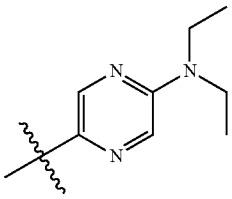
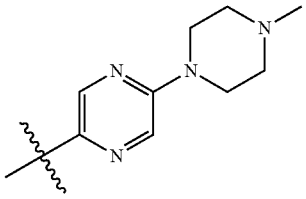
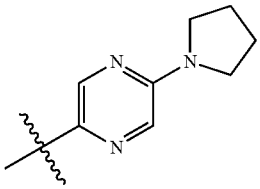
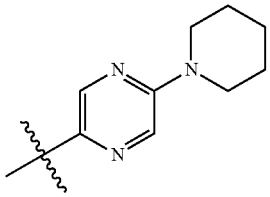
Sub-class #	B
B-50	
B-51	
B-52	
B-53	
B-54	
B-55	
B-56	
B-57	

TABLE 1-continued

Illustrative B moieties of the compounds described herein.

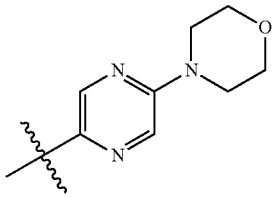
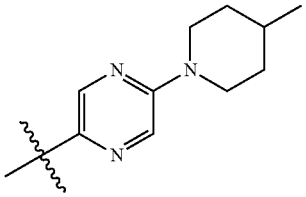
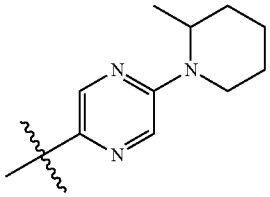
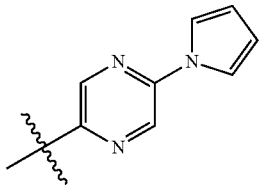
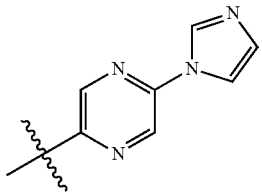
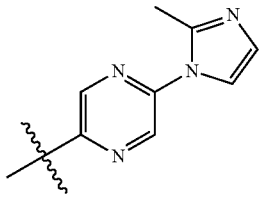
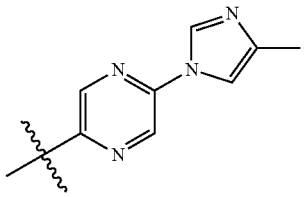
Sub-class #	B
B-58	
B-59	
B-60	
B-61	
B-62	
B-63	
B-64	

TABLE 1-continued

Illustrative B moieties of the compounds described herein.

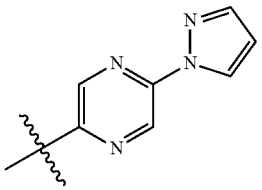
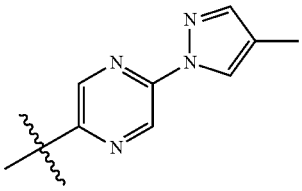
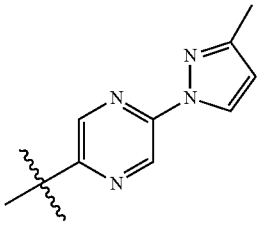
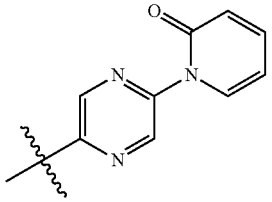
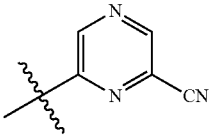
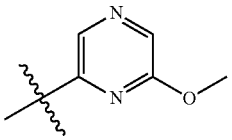
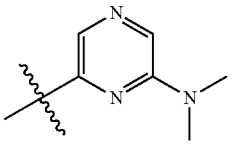
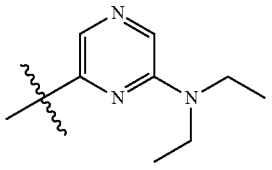
Sub-class #	B
B-65	
B-66	
B-67	
B-68	
B-69	
B-70	
B-71	
B-72	

TABLE 1-continued

Illustrative B moieties of the compounds described herein.

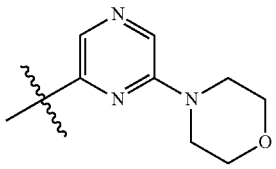
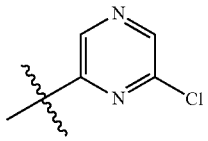
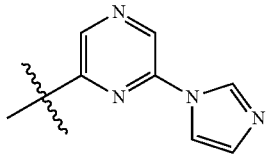
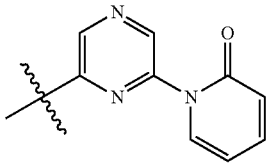
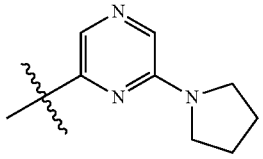
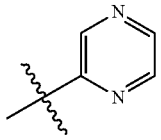
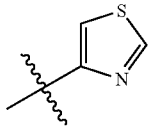
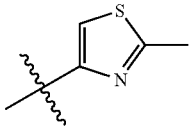
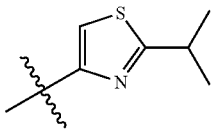
Sub-class #	B
B-73	
B-74	
B-75	
B-76	
B-77	
B-78	
B-79	
B-80	
B-81	

TABLE 1-continued

Illustrative B moieties of the compounds described herein.

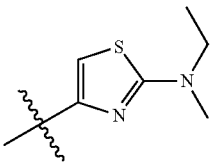
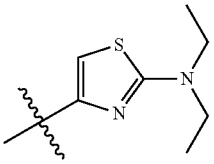
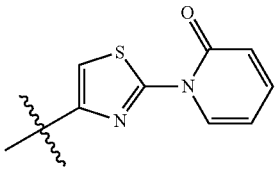
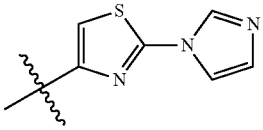
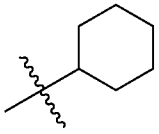
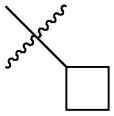
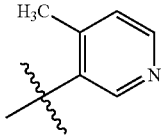
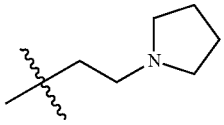
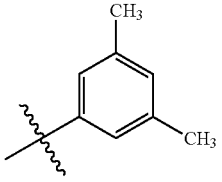
Sub-class #	B
B-82	
B-83	
B-84	
B-85	
B-86	
B-87	—CH_3
B-88	—CH_2CH_3
B-89	
B-90	
B-91	
B-92	

TABLE 1-continued

Illustrative B moieties of the compounds described herein.

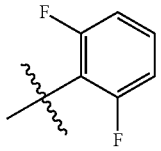
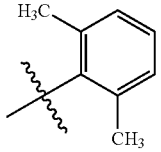
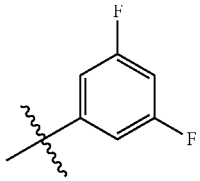
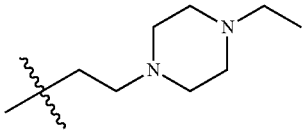
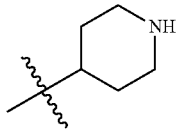
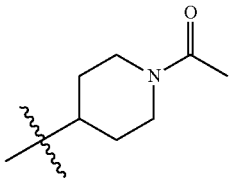
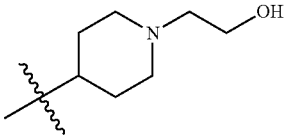
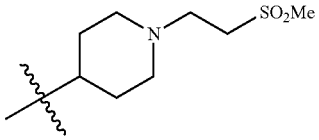
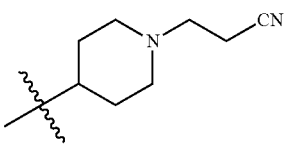
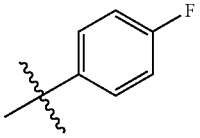
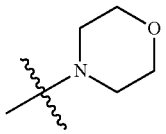
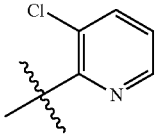
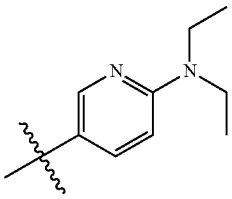
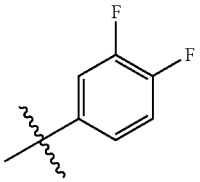
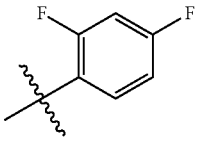
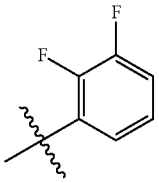
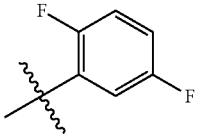
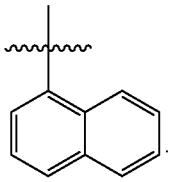
Sub-class #	B
B-93	
B-94	
B-95	
B-96	
B-97	
B-98	
B-99	
B-100	
B-101	

TABLE 1-continued

Illustrative B moieties of the compounds described herein.

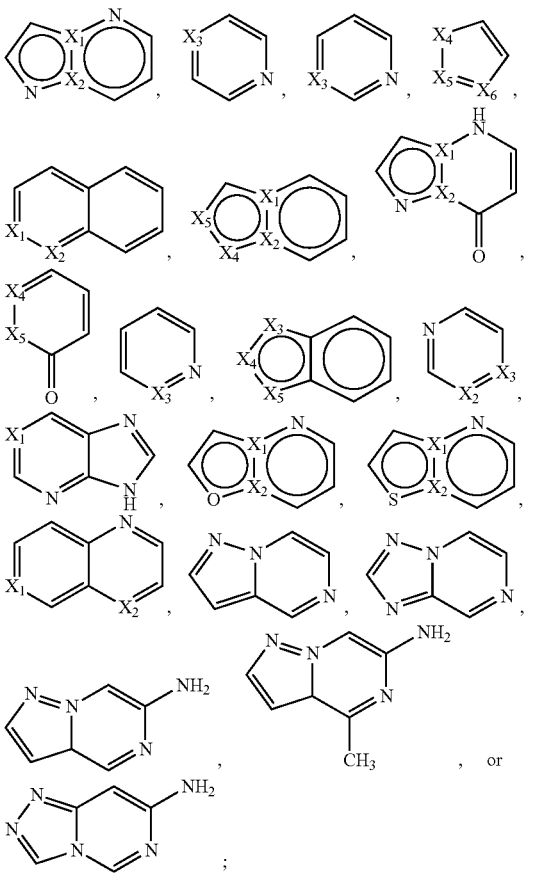
Sub-class #	B
B-102	
B-103	
B-104	
B-105	
B106	
B107	
B108	
B109	

In some embodiments, W^d is aryl (e.g., a monocyclic aryl or a bicyclic aryl). In some embodiments, W^d is substituted or unsubstituted phenyl. In some embodiments, W^d is bicyclic aryl (e.g., substituted or unsubstituted naphthyl). In some embodiments, W^d is



In certain embodiments, W^d is heteroaryl (e.g., monocyclic heteroaryl, e.g., a monocyclic 5- or 6-membered heteroaryl; or bicyclic heteroaryl, e.g., a 5/6-bicyclic heteroaryl or a 6/6-bicyclic heteroaryl).

In some embodiments, W^d is



wherein

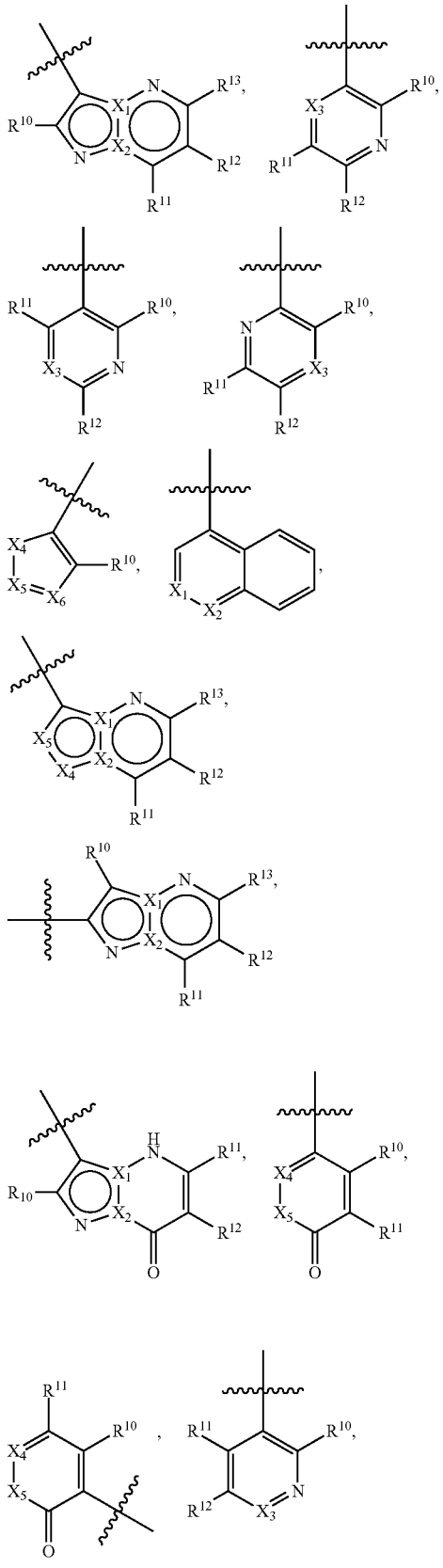
X_1, X_2 and X_3 are each independently C, CR^{13}, or N;

X_4, X_5 and X_6 are each independently N, NR^{12}, CR^{13}, S, or O; and

wherein each of the W_d group is optionally substituted with one or more of R^{10}, R^{11}, R^{12}, and R^{13}, where R^{10}, R^{11}, R^{12} and R^{13} are each independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, or NR'R" wherein R' and R" together with the nitrogen to which they are attached form a cyclic moiety; and

the point of attachment is at any open position on the W_d group.

In some embodiments, W^d is



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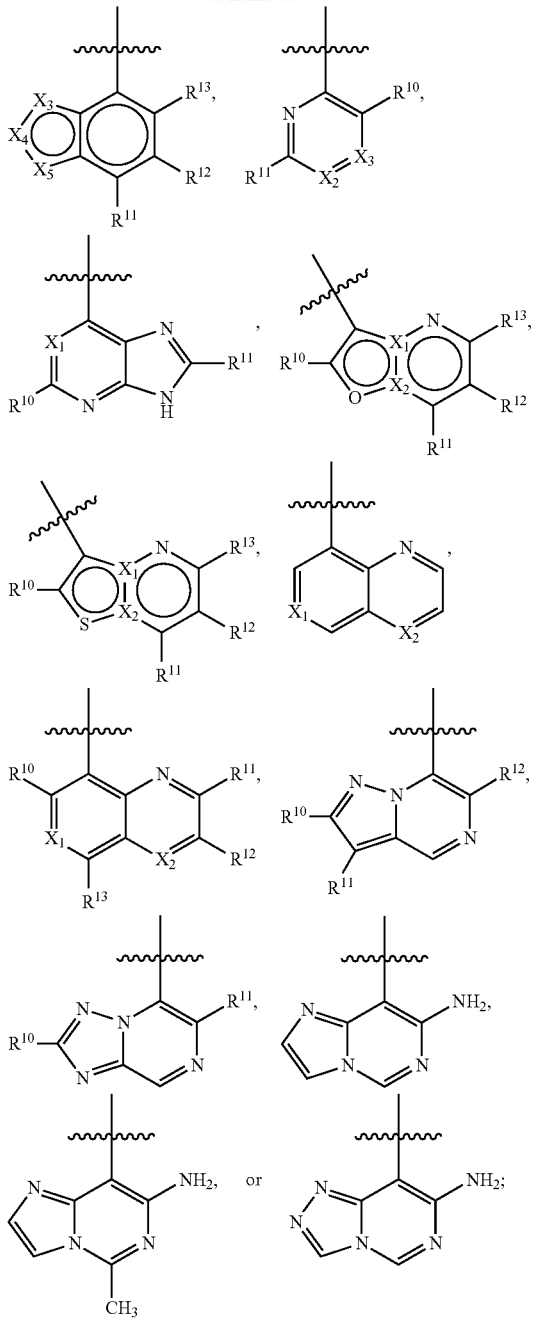


wherein

X_1, X_2 and X_3 are each independently C, CR^{13}, or N;

X_4, X_5 and X_6 are each independently N, NR^{12}, CR^{13}, S, or O; and

R^{10}, R^{11}, R^{12}, and R^{13} are each independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, or NR'R" wherein R' and R" together with the nitrogen to which they are attached form a cyclic moiety.

In certain embodiments, X_1 is N. In some embodiments, X_1 is CR^{13}. In some embodiments, X_1 is C.

In certain embodiments, X_2 is N. In some embodiments, X_2 is CR^{13}. In some embodiments, X_2 is C.

In certain embodiments, X_3 is N. In some embodiments, X_3 is CR^{13}.

In certain embodiments, X_4 is N. In some embodiments, X_4 is CR^{13}. In some embodiments, X_4 is S.

In certain embodiments, X_5 is NR^{12}. In some embodiments, X_5 is CR^{13}. In some embodiments, X_5 is O. In some embodiments, X_5 is S.

In certain embodiments, X_6 is N. In some embodiments, X_6 is NH. In some embodiments, X_6 is CR^{13}. In some embodiments, X_6 is NH. In some embodiments, X_6 is O.

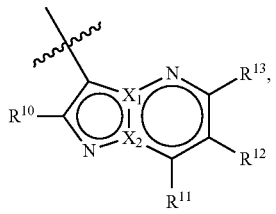
In some embodiments, each R^{10} is independently hydrogen, halo (e.g., fluoro, chloro, or bromo), cyano, hydroxyl, alkyl (e.g., methyl or CF_3), alkoxyl, amino (e.g., cycloalkylamino (e.g., cyclopropylamino), alkylamino (e.g., methylamino or dimethylamino), or NH_2), aryl (e.g., substituted or unsubstituted phenyl), heteroaryl (e.g., a 5- or 6-membered heteroaryl, e.g., pyrazolyl, pyridinyl, among others), heterocyclyl (e.g., N-morpholinyl), or amido. In some embodiments, each R^{10} is independently hydrogen, alkyl (e.g., methyl), amino (e.g., cyclopropylamino, methylamino or NH_2), heterocyclyl (e.g., N-morpholinyl), heteroaryl (e.g., 4-pyrazolyl), amido or halo (e.g., chloro). In one embodiment, R^{10} is NH_2. In one embodiment, R^{10} is H.

In certain embodiments, each R^{11} is independently hydrogen, halo (e.g., fluoro, chloro, or bromo), cyano, hydroxyl, alkyl (e.g., methyl or CF_3), alkoxyl, amino (e.g., cycloalkylamino (e.g., cyclopropylamino), alkylamino (e.g., methylamino or dimethylamino), or NH_2), aryl (e.g., substituted or unsubstituted phenyl), heteroaryl (e.g., a 5- or 6-membered heteroaryl, e.g., pyrazolyl, pyridinyl, among others), heterocyclyl (e.g., N-morpholinyl), or amido. In some embodiments, each R^{11} is independently hydrogen, amino, halo (e.g., bromo), aryl (e.g., phenyl) or alkyl (e.g., methyl). In one embodiment, R^{11} is H.

In certain embodiments, each R^{12} is independently hydrogen, halo (e.g., fluoro, chloro, or bromo), cyano, hydroxyl, alkyl (e.g., methyl or CF_3), alkoxyl, amino (e.g., cycloalkylamino (e.g., cyclopropylamino), alkylamino (e.g., methylamino or dimethylamino), or NH_2), aryl (e.g., substituted or unsubstituted phenyl), heteroaryl (e.g., a 5- or 6-membered heteroaryl, e.g., pyrazolyl, pyridinyl, among others), heterocyclyl (e.g., N-morpholinyl), or amido. In some embodiments, each R^{12} is independently hydrogen, amino, or alkyl (e.g., methyl). In one embodiment, R^{12} is H.

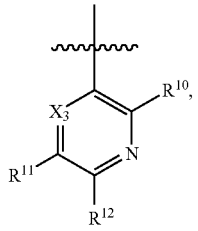
In certain embodiments, each R^{13} is independently hydrogen, halo (e.g., fluoro, chloro, or bromo), cyano, hydroxyl, alkyl (e.g., methyl or CF_3), alkoxyl, amino (e.g., cycloalkylamino (e.g., cyclopropylamino), alkylamino (e.g., methylamino or dimethylamino), or NH_2), aryl (e.g., substituted or unsubstituted phenyl), heteroaryl (e.g., a 5- or 6-membered heteroaryl, e.g., pyrazolyl, pyridinyl, among others), heterocyclyl (e.g., N-morpholinyl), or amido. In some embodiments, each R^{13} is independently hydrogen, amino (e.g., NH_2), amido (e.g., NH—C(=O)Me), or alkyl (e.g., methyl). In one embodiment, R^{13} is H.

In some embodiments, W^d is:



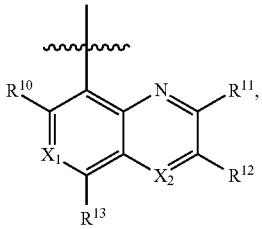
wherein one of X_1 and X_2 is C and the other is N; and R^{10}, R^{11}, R^{12}, and R^{13} are as defined herein. In some embodiments, R^{10} is hydrogen, halo (e.g., fluoro, chloro, or bromo), cyano, hydroxyl, alkyl (e.g., methyl or CF_3), alkoxyl, amino (e.g., cycloalkylamino (e.g., cyclopropylamino), alkylamino (e.g., methylamino or dimethylamino), or NH_2), aryl (e.g., substituted or unsubstituted phenyl), heteroaryl (e.g., a 5- or 6-membered heteroaryl, e.g., pyrazolyl, pyridinyl, among others), heterocyclyl (e.g., N-morpholinyl), or amido. In some embodiments, R^{10} is hydrogen, alkyl (e.g., methyl), amino (e.g., cyclopropylamino, methylamino or NH_2), heterocyclyl (e.g., N-morpholinyl), heteroaryl (e.g., 4-pyrazolyl), amido or halo (e.g., chloro). In one embodiment, R^{10} is NH_2. In one embodiment, R^{10} is H. In specific embodiment, one of X_1 and X_2 is C and the other is N; R^{10} is H or NH_2; and R^{11}, R^{12}, and R^{13} are as defined herein. In specific embodiments, all of R^{11}, R^{12}, and R^{13} are H. In specific embodiments, two of R^{11}, R^{12}, and R^{13} are H, and one of R^{11}, R^{12}, and R^{13} is alkyl (e.g., methyl or CF_3), halo, cyano, aryl (e.g., phenyl), or heteroaryl (e.g., a 5- or 6-membered heteroaryl, such as, pyridinyl, pyrimidinyl, pyrazolyl, thiazolyl, imidazolyl, among others); and in some embodiments, the aryl and heteroaryl is optionally substituted with one or more substituents, such as, for example, halo (e.g., F or Cl), cyano, hydroxyl, alkyl (e.g., methyl or CF_3), alkoxyl (e.g., methoxy, OCF_3, ethoxy, or isopropyloxy), sulfonyl (e.g., $S(O)_2Me$), sulfonamidyl (e.g., $S(O)_2NH_2$, $S(O)_2NHMe$, $S(O)_2N(Me)_2$, $S(O)_2NH$-i-Pr, $S(O)_2NH$-t-Bu, $S(O)_2NH$-c-Pr, $S(O)_2NHPh$, $S(O)_2$—N-pyrrolidinyl, $S(O)_2$—N-morpholinyl, $S(O)_2$—N-piperazinyl, $S(O)_2$-4-methyl-N-piperazinyl, $NHS(O)_2Me$, $NHS(O)_2Et$, $NHS(O)_2$-c-Pr), or sulfonylurea (e.g., $NHS(O)_2N(Me)_2$).

In some embodiments, W^d is:



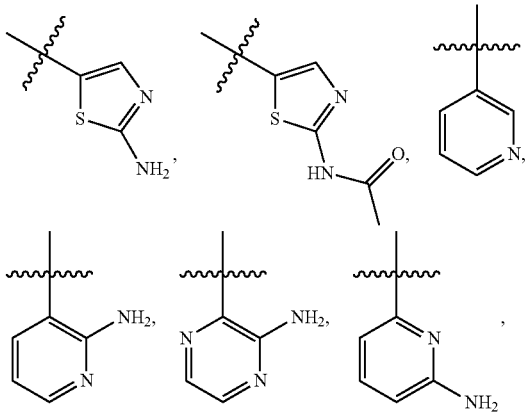
wherein X_3 is N or CR^{13}; and R^{10}, R^{11}, R^{12}, and R^{13} are as defined herein. In specific embodiments, X_3 is N or CR^{13}; R^{10} is H or NH_2; and R^{11}, R^{12}, and R^{13} are as defined herein. In specific embodiments, R^{10} is NH_2. In specific embodiments, X_3 is N. In specific embodiments, one of R^{11} and R^{12} is H, and the other is alkyl (e.g., methyl or CF_3), halo, cyano, aryl (e.g., phenyl), or heteroaryl (e.g., a 5- or 6-membered heteroaryl, such as, pyridinyl, pyrimidinyl, pyrazolyl, thiazolyl, imidazolyl, among others); and in some embodiments, the aryl and heteroaryl is optionally substituted with one or more substituents, such as, for example, halo (e.g., F or Cl), cyano, hydroxyl, alkyl (e.g., methyl or CF_3), alkoxyl (e.g., methoxy, OCF_3, ethoxy, or isopropyloxy), sulfonyl (e.g., $S(O)_2Me$), sulfonamidyl (e.g., $S(O)_2NH_2$, $S(O)_2NHMe$, $S(O)_2N(Me)_2$, $S(O)_2NH$-i-Pr, $S(O)_2NH$-t-Bu, $S(O)_2NH$-c-Pr, $S(O)_2NHPh$, $S(O)_2$—N-pyrrolidinyl, $S(O)_2$—N-morpholinyl, $S(O)_2$—N-piperazinyl, $S(O)_2$-4-methyl-N-piperazinyl, $NHS(O)_2Me$, $NHS(O)_2$-c-Pr), or sulfonylurea (e.g., $NHS(O)_2N(Me)_2$).

In some embodiments, W^d is:



wherein one of X_1 and X_2 is N and the other is CR^{13}; and R^{10}, R^{11}, R^{12}, and R^{13} are as defined herein. In specific embodiment, one of X_1 and X_2 is N and the other is CR^{13}; R^{10} is H or NH_2; and R^{11}, R^{12}, and R^{13} are as defined herein. In specific embodiments, X_1 is N and X_2 is CR^{13}. In specific embodiments, X_1 is N and X_2 is CH. In specific embodiments, R^{10} is NH_2. In specific embodiments, R^{11}; R^{12} and R^{13} are H. In specific embodiments, at least one of R^{11}, R^{12} and R^{13} is not H. In specific embodiments, one occurrence of R is not H and the other occurrences of R^{11}, R^{12} and R^{13} are H, and the one occurrence of R^{11}, R^{12} and R^{13} (which is not hydrogen) is alkyl (e.g., methyl or CF_3), halo, cyano, aryl (e.g., phenyl), or heteroaryl (e.g., a 5- or 6-membered heteroaryl, such as, pyridinyl, pyrimidinyl, pyrazolyl, thiazolyl, imidazolyl, among others); and in some embodiments, the aryl and heteroaryl is optionally substituted with one or more substituents, such as, for example, halo (e.g., F or Cl), cyano, hydroxyl, alkyl (e.g., methyl or CF_3), alkoxyl (e.g., methoxy, OCF_3, ethoxy, or isopropyloxy), sulfonyl (e.g., $S(O)_2Me$), sulfonamidyl (e.g., $S(O)_2NH_2$, $S(O)_2NHMe$, $S(O)_2N(Me)_2$, $S(O)_2NH$-i-Pr, $S(O)_2NH$-t-Bu, $S(O)_2NH$-c-Pr, $S(O)_2NHPh$, $S(O)_2$—N-pyrrolidinyl, $S(O)_2$—N-morpholinyl, $S(O)_2$—N-piperazinyl, $S(O)_2$-4-methyl-N-piperazinyl, $NHS(O)_2Me$, $NHS(O)_2$-c-Pr), or sulfonylurea (e.g., $NHS(O)_2N(Me)_2$).

In exemplary embodiments, W^d is one of the following moieties:



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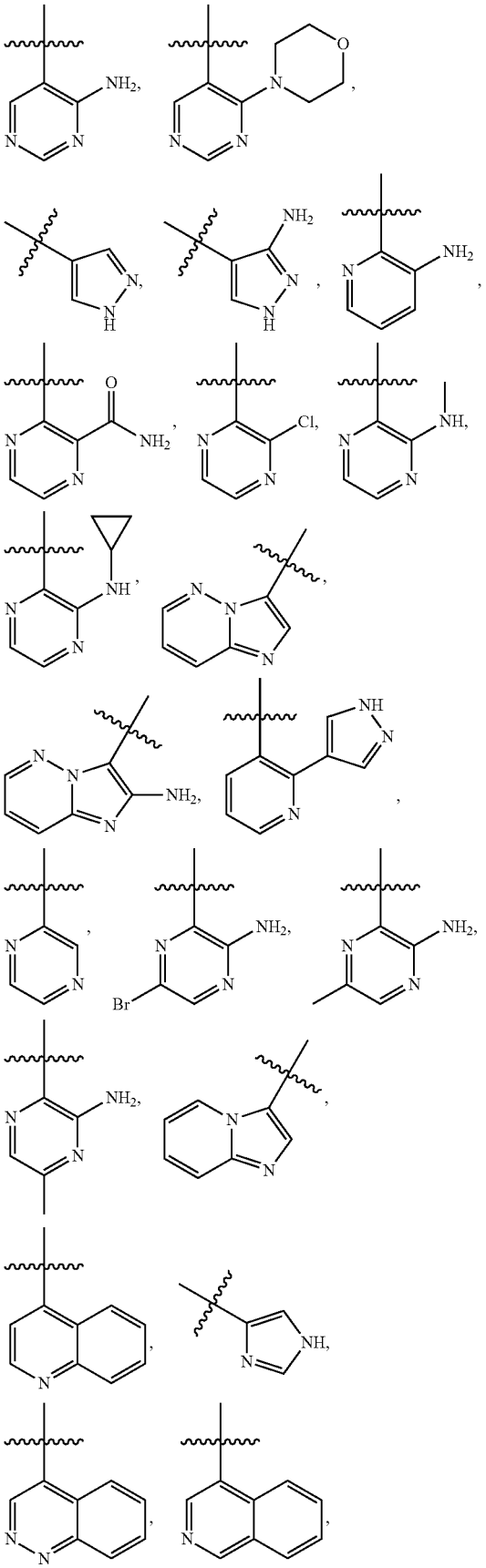

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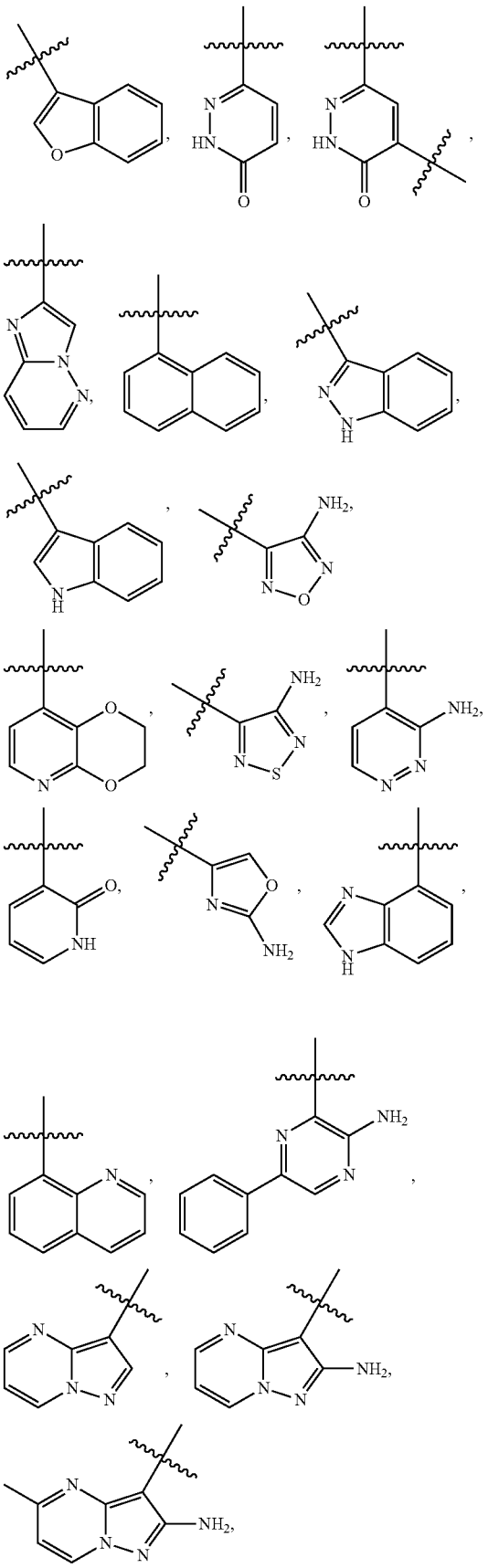

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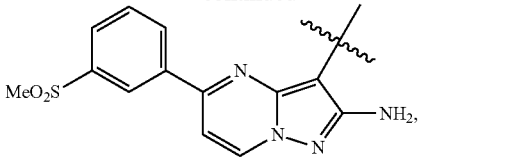

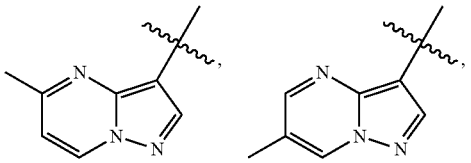

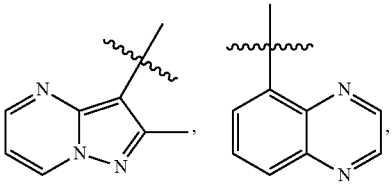

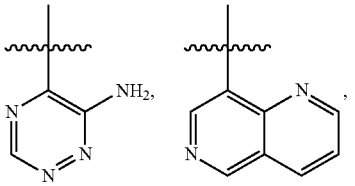

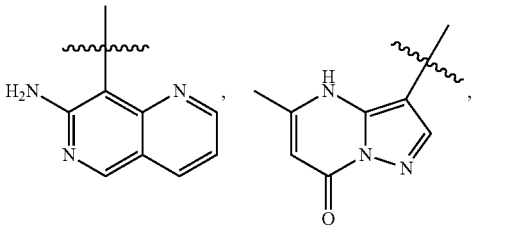

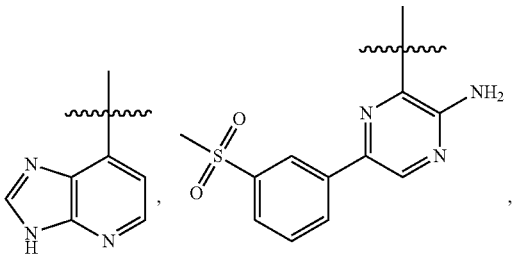

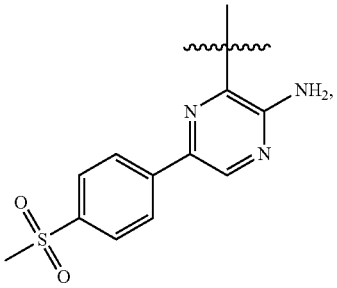

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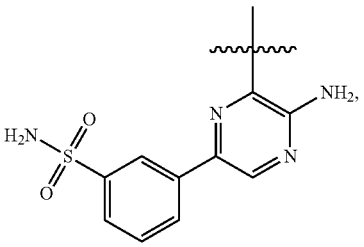

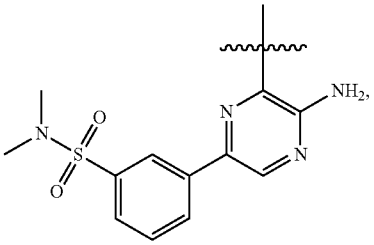

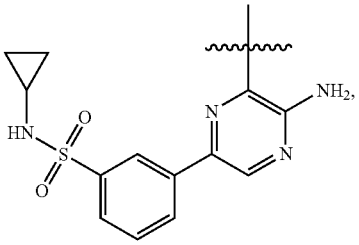

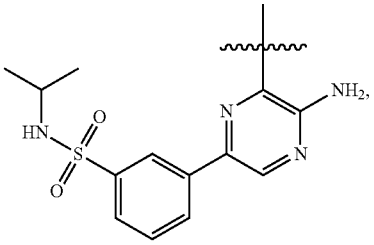

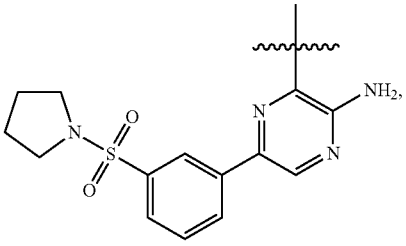

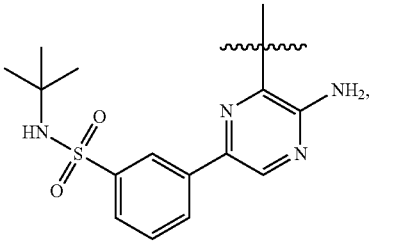

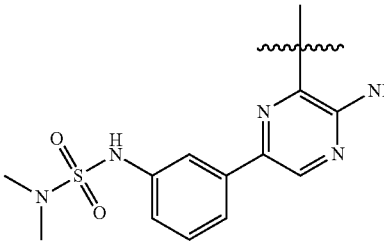

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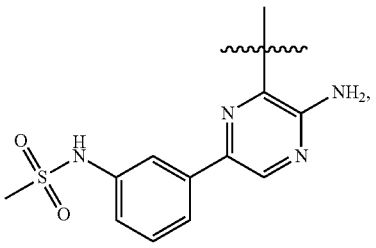

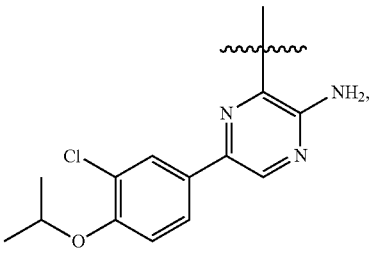

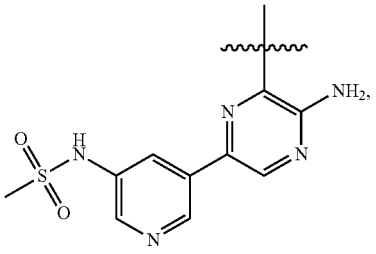

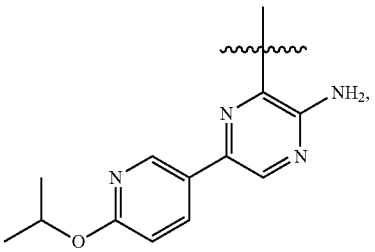

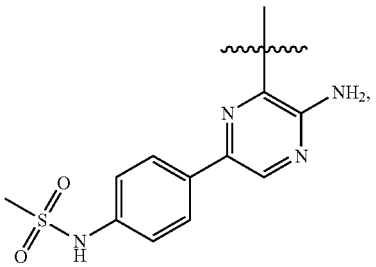

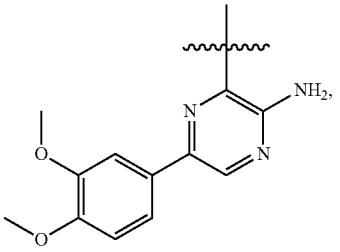

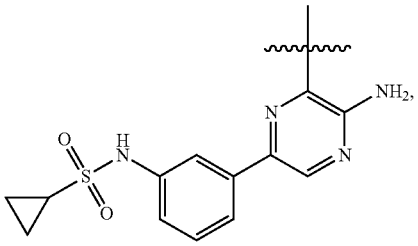

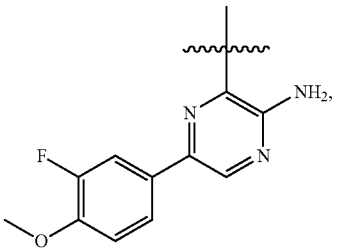

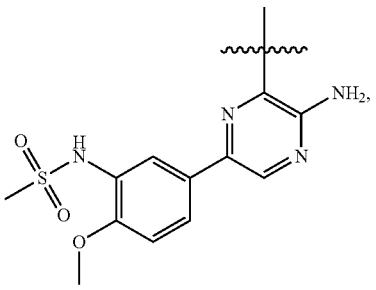

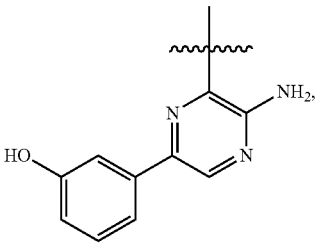

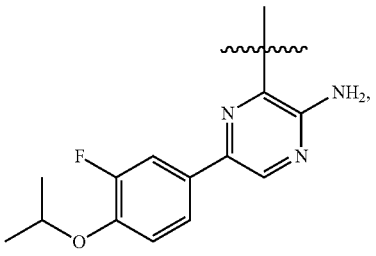

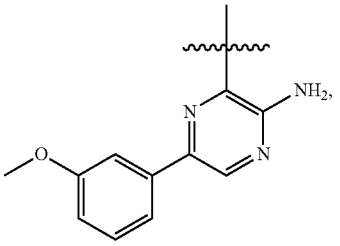

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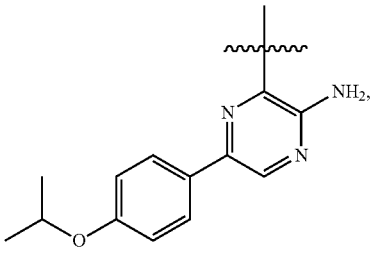
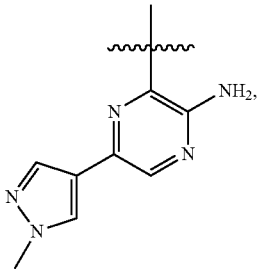
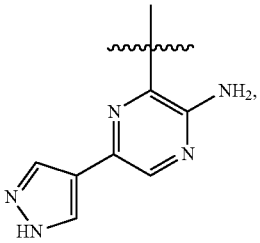
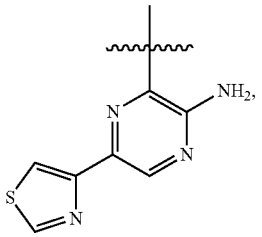
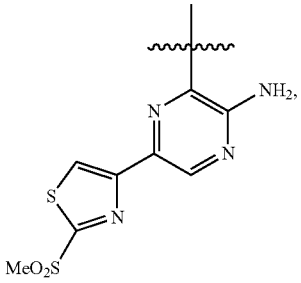
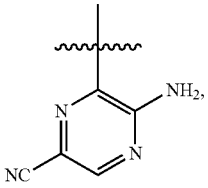


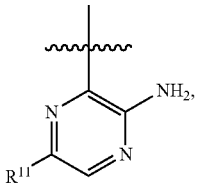




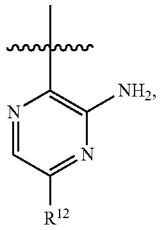






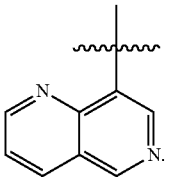


or

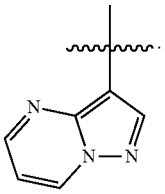


wherein R^{11} and R^{12} are as defined herein.

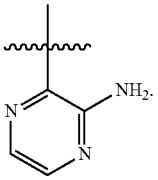
In some embodiments, W^d is



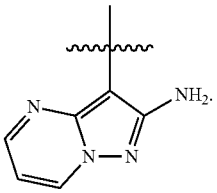
In some embodiments, W^d is



In some embodiments, W^d is

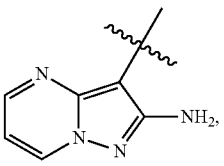


In some embodiments, W^d is



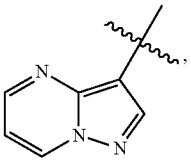
In some embodiments, X is CH. In some embodiments, X is N.

In some embodiments, in Formula (I"), (I'), or (I), when X is CH, B is unsubstituted phenyl, and W_d is



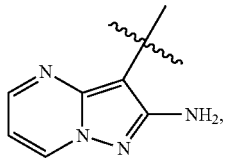
then R^1 is not hydrogen, $Si(CH_3)_3$, $CH_2Si(CH_3)_3$, methyl, $(CH_2)NH_2$, $(CH_2)_2NH_2$, $(CH_2)NHSO_2CH_3$, or $(CH_2)_nNHC(O)R^{1x}$; n is 1 or 2; R^{1x} is methyl, C_2 alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl, where the alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl is optionally substituted with one or two groups independently selected from oxo and cyano.

In some embodiments, in Formula (I"), (I'), or (I), when X is CH, B is unsubstituted phenyl, and W^d is



then R^1 is not $(CH_2)_nNHC(O)R^{1x}$; n is 1; R^{1x} is tetrahydrofuranyl or pyrrolidinyl, where the tetrahydrofuranyl or pyrrolidinyl is optionally substituted with oxo.

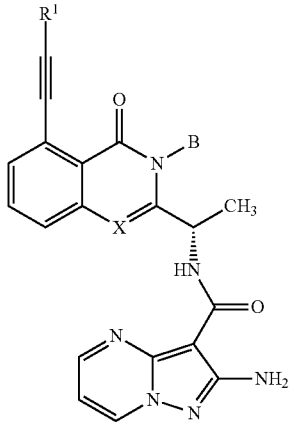
In some embodiments. in Formula (A"), (A'), or (A), when X is CH, B is unsubstituted phenyl, and W^d is



then R^1 is not phenyl.

In some embodiments, the compound is a compound of formula II:

II



wherein R^1, B, and X are as defined herein. In some embodiments, R^1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, or —$CONR^4R^5$; B is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, —$CONR^4R^5$, or —$Si(R^6)_3$;

wherein R^2, R^3, R^4, R^5, and R^6 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

X is CR^{1a} or N;

wherein R^{1a} is hydrogen, halo, alkyl, alkenyl, alkynyl, or CN;

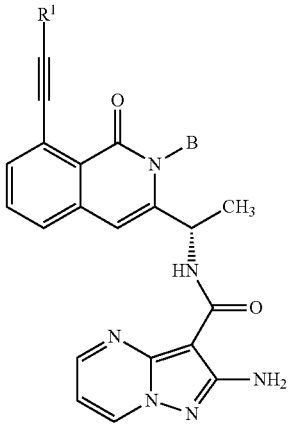
wherein each alkyl, alkenyl, or alkynyl is optionally substituted with one or more halo, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), $S(O)_2$(alkyl), cycloalkyl, heterocycloalkyl, aryl or heteroaryl;

wherein each cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with one or more halo, alkyl, alkenyl, alkynyl, OH, alkoxy, oxo, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), or $S(O)_2$(alkyl); and

wherein when X is CH, and B is unsubstituted phenyl, then R^1 is not hydrogen, $Si(CH_3)_3$, $CH_2Si(CH_3)_3$, methyl, $(CH_2)NH_2$, $(CH_2)_2NH_2$, $(CH_2)NHSO_2CH_3$, or $(CH_2)_nNHC(O)R^{1x}$; n is 1 or 2; R^{1x} is methyl, C_2 alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl, where the alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl is optionally substituted with one or two groups independently selected from oxo and cyano.

In some embodiments, the compound is a compound of formula III:

III



wherein R^1 and B are defined herein. In some embodiments, R^1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, or —$CONR^4R^5$;

B is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, —$CONR^4R^5$, or —$Si(R^6)_3$;

wherein R^2, R^3, R^4, R^5, and R^6 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

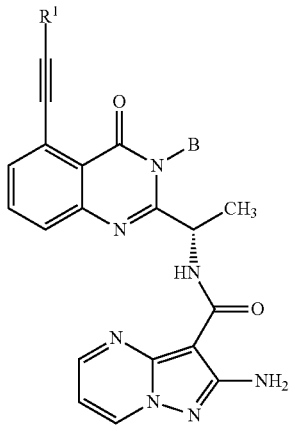
wherein each alkyl, alkenyl, or alkynyl is optionally substituted with one or more halo, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), $S(O)_2$(alkyl), cycloalkyl, heterocycloalkyl, aryl or heteroaryl;

wherein each cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with one or more halo, alkyl, alkenyl, alkynyl, OH, alkoxy, oxo, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), or $S(O)_2$(alkyl); and

wherein when B is unsubstituted phenyl, then R^1 is not hydrogen, $Si(CH_3)_3$, $CH_2Si(CH_3)_3$, methyl, $(CH_2)NH_2$, $(CH_2)_2NH_2$, $(CH_2)NHSO_2CH_3$, or $(CH_2)_nNHC(O)R^{1x}$; n is 1 or 2; R^{1x} is methyl, C_2 alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl, where the alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl is optionally substituted with one or two groups independently selected from oxo and cyano.

In some embodiments, the compound is a compound of formula IV:

IV



wherein R^1 and B are as defined herein. In some embodiments, R^1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, or —$CONR^4R^5$;

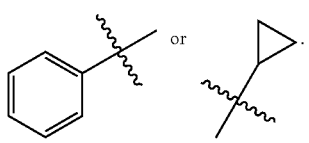
B is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, —$CONR^4R^5$, or —$Si(R^6)_3$;

wherein R^2, R^3, R^4, R^5, and R^6 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

wherein each alkyl, alkenyl, or alkynyl is optionally substituted with one or more halo, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), $S(O)_2$(alkyl), cycloalkyl, heterocycloalkyl, aryl or heteroaryl; and

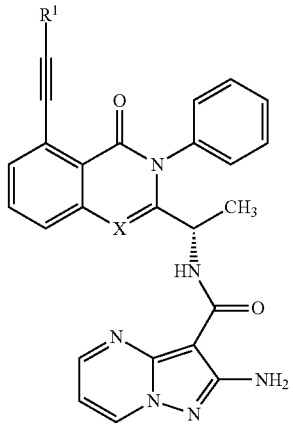
wherein each cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with one or more halo, alkyl, alkenyl, alkynyl, OH, alkoxy, oxo, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), or $S(O)_2$(alkyl).

In some embodiments of formula II, III, and W, B is phenyl substituted with 0, 1, 2, or 3 occurrence(s) of R^Z. In some embodiments, B is unsubstituted phenyl. In some embodiments, B is phenyl substituted with 1 or 2 occurrence(s) of R^Z. In some embodiments, R^Z is halo or alkyl. In some embodiments, B is methyl, isopropyl, or cyclopropyl. In some embodiments, B is cyclohexyl or optionally substituted alkyl. In some embodiments, B is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl. In some embodiments, B is 5- or 6-membered aryl or 3- to 6-membered cycloalkyl. In some embodiments, B is



In some embodiments, the compound is a compound of formula V:

V



wherein R^1 and X are as defined herein. In some embodiments, R^1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, or —$CONR^4R^5$;

wherein R^2, R^3, R^4, and R^5 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

X is CR^{1a} or N;

wherein R^{1a} is hydrogen, halo, alkyl, alkenyl, alkynyl, or CN;

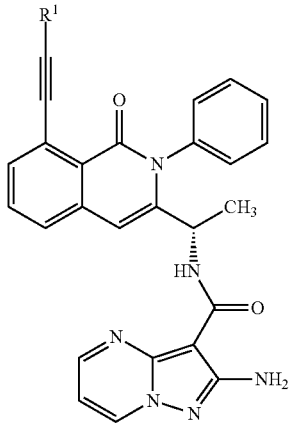
wherein each alkyl, alkenyl, or alkynyl is optionally substituted with one or more halo, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), $S(O)_2$(alkyl), cycloalkyl, heterocycloalkyl, aryl or heteroaryl;

wherein each cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with one or more halo, alkyl, alkenyl, alkynyl, OH, alkoxy, oxo, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), or $S(O)_2$(alkyl); and

wherein when X is CH, then R^1 is not hydrogen, $Si(CH_3)_3$, $CH_2Si(CH_3)_3$, methyl, $(CH_2)NH_2$, $(CH_2)_2NH_2$, $(CH_2)NHSO_2CH_3$, or $(CH_2)_nNHC(O)R^{1x}$; n is 1 or 2; R^{1x} is methyl, C_2 alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl, where the alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl is optionally substituted with one or two groups independently selected from oxo and cyano.

In some embodiments, the compound is a compound of formula VI:

VI



wherein R^1 is as defined herein. In some embodiments, R^1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, or —$CONR^4R^5$;

wherein R^2, R^3, R^4, and R^5 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

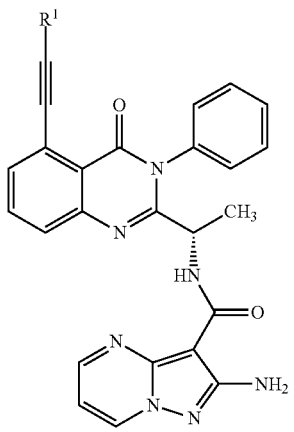
wherein each alkyl, alkenyl, or alkynyl is optionally substituted with one or more halo, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), $S(O)_2$(alkyl), cycloalkyl, heterocycloalkyl, aryl or heteroaryl;

wherein each cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with one or more halo, alkyl, alkenyl, alkynyl, OH, alkoxy, oxo, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), or $S(O)_2$(alkyl); and

wherein R^1 is not hydrogen, $Si(CH_3)_3$, $CH_2Si(CH_3)_3$, methyl, $(CH_2)NH_2$, $(CH_2)_2NH_2$, $(CH_2)NHSO_2CH_3$, or $(CH_2)_nNHC(O)R^{1x}$; n is 1 or 2; R^{1x} is methyl, C_2 alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl, where the alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl is optionally substituted with one or two groups independently selected from oxo and cyano;

In some embodiments, the compound is a compound of formula VII:

VII



wherein R^1 is as defined herein. In some embodiments, R^1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, or —$CONR^4R^5$;

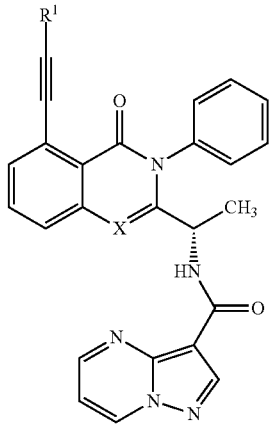
wherein R^2, R^3, R^4, and R^5 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

wherein each alkyl, alkenyl, or alkynyl is optionally substituted with one or more halo, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), $S(O)_2$(alkyl), cycloalkyl, heterocycloalkyl, aryl or heteroaryl; and

wherein each cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with one or more halo, alkyl, alkenyl, alkynyl, OH, alkoxy, oxo, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), or $S(O)_2$(alkyl).

In some embodiments, the compound is a compound of formula VIII:

VIII



wherein X and R^1 are as defined herein. In some embodiments, R^1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, or —$CONR^4R^5$;

wherein R^2, R^3, R^4, and R^5 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

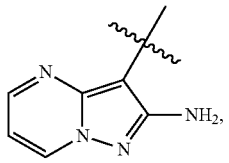
X is CR^{1a} or N;

wherein R^{1a} is hydrogen, halo, alkyl, alkenyl, alkynyl, or CN;

wherein each alkyl, alkenyl, or alkynyl is optionally substituted with one or more halo, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), $S(O)_2$(alkyl), cycloalkyl, heterocycloalkyl, aryl or heteroaryl;

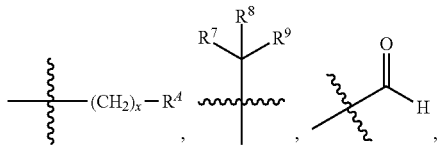
wherein each cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with one or more halo, alkyl, alkenyl, alkynyl, OH, alkoxy, oxo, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), or $S(O)_2$(alkyl); and

wherein when X is CH and W^d is



then R^1 is not hydrogen, $Si(CH_3)_3$, $CH_2Si(CH_3)_3$, methyl, $(CH_2)NH_2$, $(CH_2)_2NH_2$, $(CH_2)NHSO_2CH_3$, or $(CH_2)_nNHC(O)R^{1x}$; n is 1 or 2; R^{1x} is methyl, C_2 alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl, where the alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl is optionally substituted with one or two groups independently selected from oxo and cyano.

In some embodiments of formulas II-VIII, R^1 is branched alkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, 5- or 6-membered cycloalkyl, or 5- or 6-membered heterocycloalkyl,



cyclopropyl, or methyl,

wherein R^A is OH, alkoxy, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

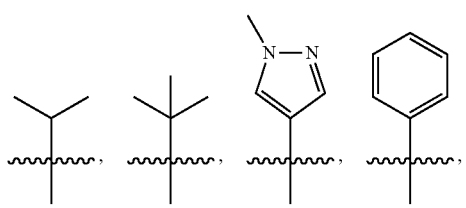
x is 1, 2, 3, 4, 5, or 6;

R^7, R^8, and R^9 are each, independently, hydrogen, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

In some embodiments, R^A is hydroxyl, alkoxy or heterocycloalkyl. In some embodiments, R^7, R^8, and R^9 are, independently, alkyl of 1-4 carbons, amino, hydroxyl, or alkoxy of 1-4 carbons.

In certain embodiments, R^1 is a 5- to 10-membered heteroaryl. In certain embodiments, R^1 is a 5- to 6-membered heteroaryl. In certain embodiments, R^1 is a 6-membered heteroaryl. In certain embodiments, R^1 is a pyridinyl. In certain embodiments, R^1 is a pyrimidinyl. In certain embodiments, R^1 is a 5-membered heteroaryl. In certain embodiments, R^1 is a thiazolyl. In certain embodiments, R^1 is a pyrazolyl. In certain embodiments, R^1 is an imidazolyl. In certain embodiments, the heteroaryl is substituted with one or more alkyl.

In some embodiments of formulas II-VIII, R^1 is: methyl,



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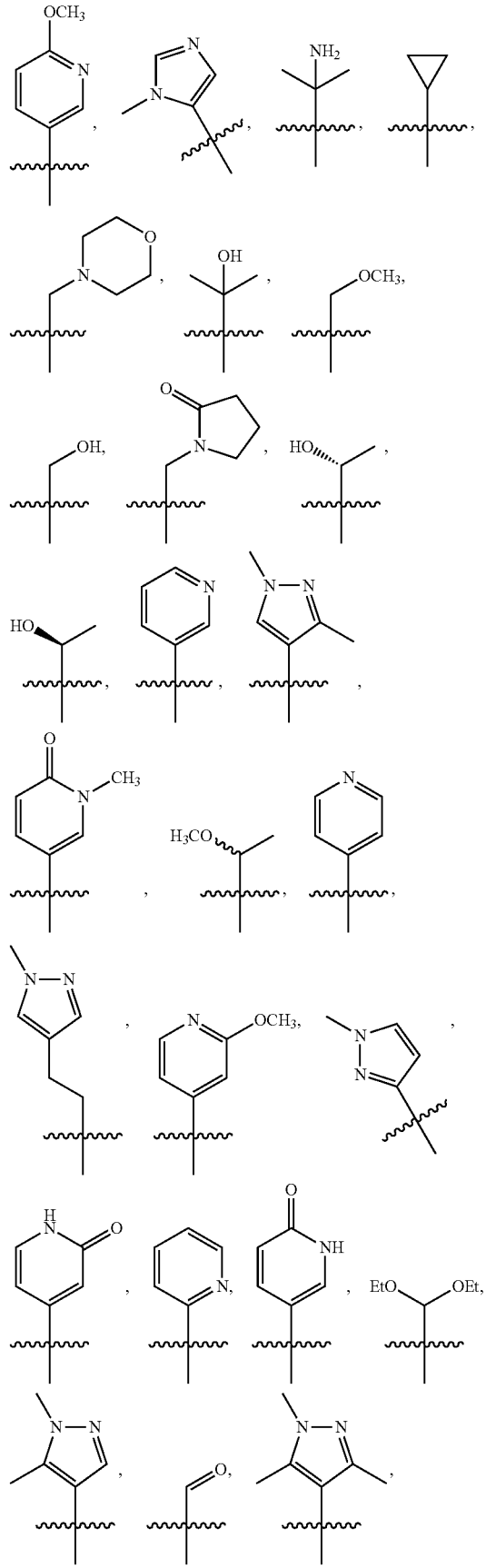

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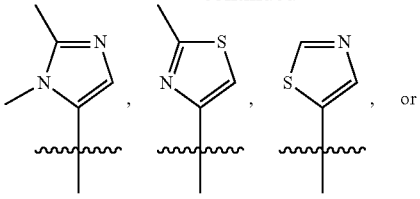
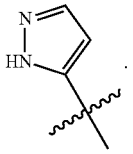
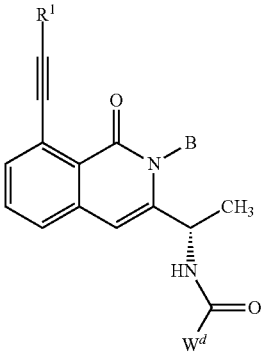




In some embodiments, the compound is a compound of formula IX:



IX

wherein R^1, B, and W^d are as defined herein. In some embodiments, R^1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, or —$CONR^4R^5$;

B is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, —$CONR^4R^5$, or —$Si(R^6)_3$;

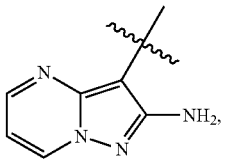
wherein R^2, R^3, R^4, R^5, and R^6 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

W^d is heteroaryl, cycloalkyl, heterocycloalkyl, or aryl; and

wherein each alkyl, alkenyl, or alkynyl is optionally substituted with one or more halo, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), $S(O)_2$(alkyl), cycloalkyl, heterocycloalkyl, aryl or heteroaryl;

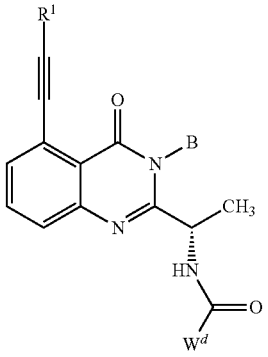
wherein each cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with one or more halo, alkyl, alkenyl, alkynyl, OH, alkoxy, oxo, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), $S(O)_2$(alkyl); and

wherein when B is unsubstituted phenyl and W^d is



then R^1 is not hydrogen, $Si(CH_3)_3$, $CH_2Si(CH_3)_3$, methyl, $(CH_2)NH_2$, $(CH_2)_2NH_2$, $(CH_2)NHSO_2CH_3$, or $(CH_2)_nNHC(O)R^{1x}$; n is 1 or 2; R^{1x} is methyl, C_2 alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl, where the alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl is optionally substituted with one or two groups independently selected from oxo and cyano.

In some embodiments, the compound is a compound of formula X:



X

wherein R^1, B, and W^d are as defined herein. In some embodiments, R^1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, or —$CONR^4R^5$;

B is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, —$CONR^4R^5$, or —$Si(R^6)_3$;

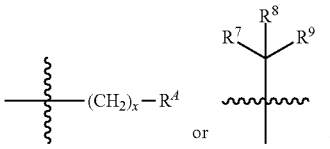
wherein R^2, R^3, R^4, R^5, and R^6 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

W^d is heteroaryl, cycloalkyl, heterocycloalkyl, or aryl; and

wherein each alkyl, alkenyl, or alkynyl is optionally substituted with one or more halo, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), $S(O)_2$(alkyl), cycloalkyl, heterocycloalkyl, aryl or heteroaryl; and

wherein each cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with one or more halo, alkyl, alkenyl, alkynyl, OH, alkoxy, oxo, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), or $S(O)_2$(alkyl).

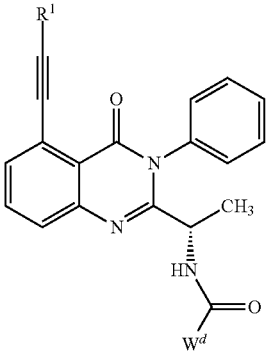
In some embodiments of formulas I-X, R^1 is



wherein R^A and R^7-R^9 are as defined herein.

In certain embodiments, R^1 is a 5- to 10-membered heteroaryl. In certain embodiments, R^1 is a 5- to 6-membered heteroaryl. In certain embodiments, R^1 is a 6-membered heteroaryl. In certain embodiments, R^1 is a pyridinyl. In certain embodiments, R^1 is a pyrimidinyl. In certain embodiments, R^1 is a 5-membered heteroaryl. In certain embodiments, R^1 is a thiazolyl. In certain embodiments, R^1 is a pyrazolyl. In certain embodiments, R^1 is an imidazolyl. In certain embodiments, the heteroaryl is substituted with one or more alkyl.

In some embodiments, the compound is a compound of formula XI:



XI

wherein R^1 and W^d are as defined herein. In some embodiments, R^1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, or —$CONR^4R^5$;

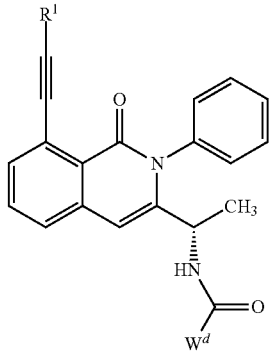
wherein R^2, R^3, R^4, and R^5 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

W^d is heteroaryl, cycloalkyl, heterocycloalkyl, or aryl; and

wherein each alkyl, alkenyl, or alkynyl is optionally substituted with one or more halo, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), $S(O)_2$(alkyl), cycloalkyl, heterocycloalkyl, aryl or heteroaryl; and

wherein each cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with one or more halo, alkyl, alkenyl, alkynyl, OH, alkoxy, oxo, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), or $S(O)_2$(alkyl).

In some embodiments, the compound is a compound of formula XII:



XII

wherein R^1 and W^d are as defined herein. In some embodiments, R^1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, or —$CONR^4R^5$;

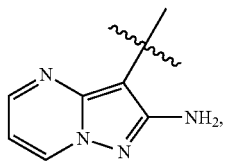
wherein R^2, R^3, R^4, and R^5 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

W^d is heteroaryl, cycloalkyl, heterocycloalkyl, or aryl; and

wherein each alkyl, alkenyl, or alkynyl is optionally substituted with one or more halo, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), $S(O)_2$(alkyl), cycloalkyl, heterocycloalkyl, aryl or heteroaryl;

wherein each cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with one or more halo, alkyl, alkenyl, alkynyl, OH, alkoxy, oxo, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), or $S(O)_2$(alkyl); and

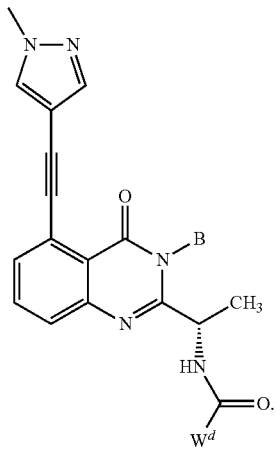
wherein when W^d is



then R^1 is not hydrogen, $Si(CH_3)_3$, $CH_2Si(CH_3)_3$, methyl, $(CH_2)NH_2$, $(CH_2)_2NH_2$, $(CH_2)NHSO_2CH_3$, or $(CH_2)_nNHC(O)R^{1x}$; n is 1 or 2; R^{1x} is methyl, C_2 alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl, where the alkene, cyclohexyl, cyclopentyl, tetrahydrofuranyl, furanyl, or pyrrolidinyl is optionally substituted with one or two groups independently selected from oxo and cyano

In some embodiments, the compound is a compound of formula XIII,

XIII



wherein B and W^d are as defined herein. In some embodiments, B is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, —$CONR^4R^5$, or —$Si(R^6)_3$;

wherein R^2, R^3, R^4, R^5, and R^6 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

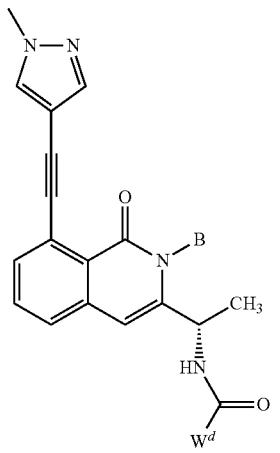
W^d is heteroaryl, cycloalkyl, heterocycloalkyl, or aryl; and

wherein each alkyl, alkenyl, or alkynyl is optionally substituted with one or more halo, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), $S(O)_2$(alkyl), cycloalkyl, heterocycloalkyl, aryl or heteroaryl; and

wherein each cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with one or more halo, alkyl, alkenyl, alkynyl, OH, alkoxy, oxo, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), or $S(O)_2$(alkyl).

In some embodiments, the compound is a compound of formula XIV:

XIV



wherein B and W^d are as defined herein. In some embodiments, B is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, —$CONR^4R^5$, or —$Si(R^6)_3$;

wherein R^2, R^3, R^4, R^5, and R^6 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

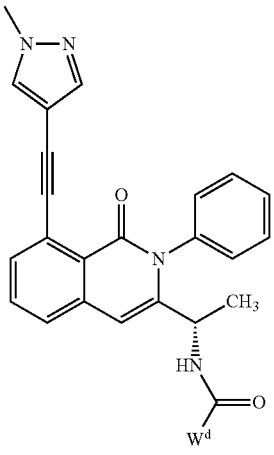
W^d is heteroaryl, cycloalkyl, heterocycloalkyl, or aryl; and

wherein each alkyl, alkenyl, or alkynyl is optionally substituted with one or more halo, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), $S(O)_2$(alkyl), cycloalkyl, heterocycloalkyl, aryl or heteroaryl; and

wherein each cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with one or more halo, alkyl, alkenyl, alkynyl, OH, alkoxy, oxo, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), or $S(O)_2$(alkyl).

In some embodiments, the compound is a compound of formula XV:

XV

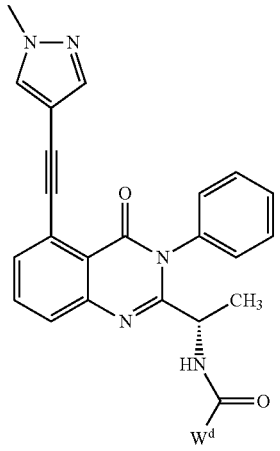


wherein W^d is as defined herein. In some embodiments, W^d is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and

wherein each cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with one or more halo, alkyl, alkenyl, alkynyl, OH, alkoxy, oxo, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), or $CON(alkyl)_2$.

In some embodiments, the compound is a compound of formula XVI:

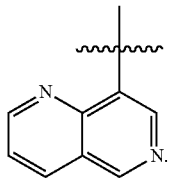
XVI



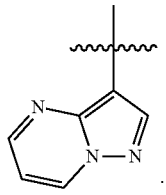
wherein W^d is defined herein. In some embodiments, W^d is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and

wherein each cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with one or more halo, alkyl, alkenyl, alkynyl, OH, alkoxy, oxo, NH_2, NH(alkyl), N(alkyl)$_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), or CON(alkyl)$_2$.

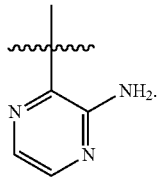
In some embodiments of formulas IX-XVI, W^d is



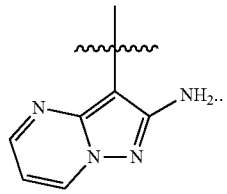
In some embodiments of formulas IX-XVI, W^d is



In some embodiments of formulas IX-XVI, W^d is



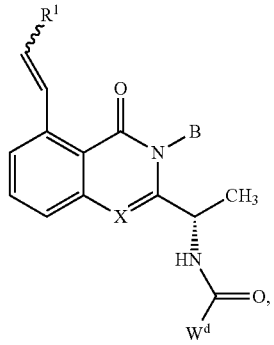
In some embodiments of formulas IX-XVI, W^d is



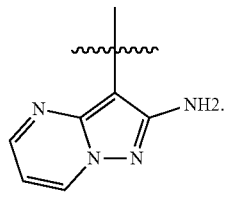
In some embodiments of formulas R^1 is not hydrogen. In some embodiments of formulas I-XII, R^1 is not linear alkyl or hydrogen. In some embodiments of formulas R^1 is not linear C_1-C_3 alkyl or hydrogen. In some embodiments of formulas R^1 is not methyl or hydrogen.

In certain embodiments, provided herein are compounds of Formula (A):

Formula (A)



or a pharmaceutically acceptable form thereof, wherein R^1, B, W^d and X are as defined herein. In certain embodiments, R^1 is alkyl or heteroaryl. In certain embodiments, R^1 is heteroaryl. In certain embodiments, R^1 is alkyl. In certain embodiments, B is phenyl. In certain embodiments, X is CH or N. In certain embodiments, X is CH.

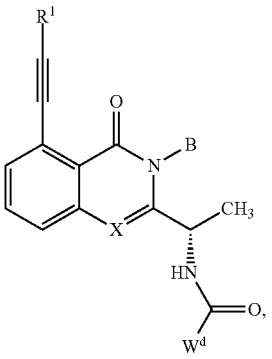


In certain embodiments, X is N. In certain embodiments, W^d is

In certain embodiments, the compound of formula (A"), (A'), or (A) is a mixture of trans and cis (e.g., where R^1 is trans or cis). In certain embodiments, R^1 is trans. In certain embodiments, R^1 is cis. In certain embodiments, the percentage of trans to cis is about 50%, greater than about 50%, greater than about 55%, greater than about 60%, greater than about 65%, greater than about 70%, greater than about 75%, greater than about 80%, greater than about 85%, greater than about 90%, greater than about 95%, greater than about 96%, greater than about 97%, greater than about 98%, or greater than about 99%.

In one embodiment, provided herein is a compound of Formula XVII:

Formula XVII



wherein:

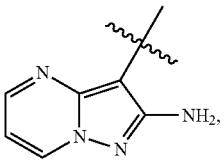
R^1 and B are each, independently, linear or branched alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, —COR^2, —$COOR^3$, —$CONR^4R^5$, or —$Si(R^6)_3$;

wherein R^2, R^3, R^4, R^5, and R^6 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

W^d is heteroaryl, cycloalkyl, heterocycloalkyl, or aryl; and

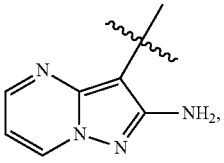
X is CH or N;

wherein when X is CH, B is unsubstituted phenyl, W^d is



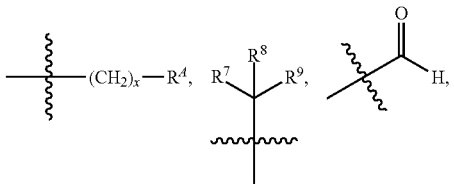
and R^1 is a linear alkyl, then the linear alkyl contains at least three consecutively bonded carbons;

wherein when X is CH, B is unsubstituted phenyl, and W^d is



then R^1 is not $Si(CH_3)_3$; or a pharmaceutically acceptable form thereof.

In some embodiments of Formula XVII, R^1 is branched alkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, 5- or 6-membered cycloalkyl, or 5- to 6-membered heterocycloalkyl,



cyclopropyl, or methyl,

wherein R^A is hydroxyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

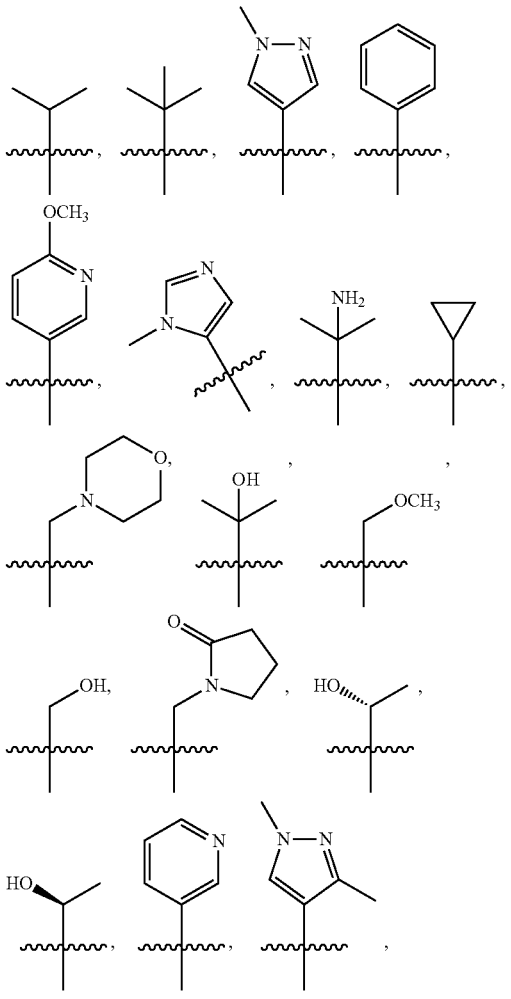
x is 1, 2, 3, 4, 5 or 6;

R^7, R^8, and R^9 are each, independently, hydrogen, hydroxyl, alkoxy, amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein at least two of R^7, R^8, and R^9 are not hydrogen.

In some embodiments of Formula XVII, R^A is hydroxyl, alkoxy or heterocycloalkyl.

In some embodiments of Formula XVII, R^7, R^8, and R^9 are, independently, alkyl of 1-4 carbons, amino, hydroxyl, or alkoxy of 1-4 carbons.

In some embodiments of Formula XVII, R_1 is: methyl,



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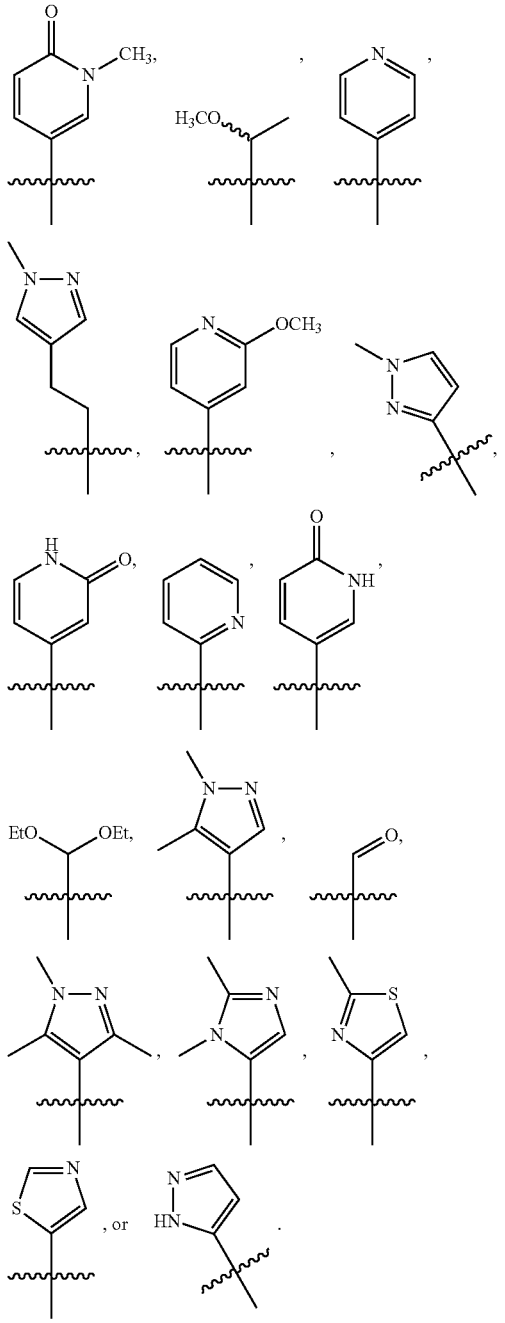
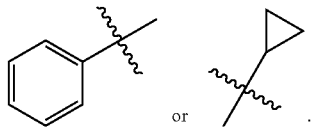


In some embodiments of Formula XVII, B is phenyl substituted with 0, 1, 2, or 3 occurrence(s) of R^z. In some embodiments, B is unsubstituted phenyl. In some embodiments, B is phenyl substituted with 1 or 2 occurrence(s) of R^Z. In some embodiments, R^Z is halo or alkyl. In some embodiments, B is methyl, isopropyl, or cyclopropyl. In some embodiments, B is cyclohexyl or optionally substituted alkyl.

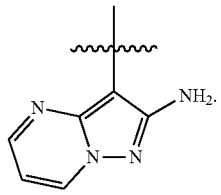
In some embodiments of Formula XVII, B is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl.

In some embodiments of Formula XVII, B is 5- or 6-membered aryl or 3-6-membered cycloalkyl.

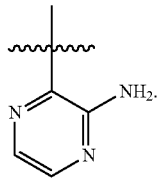
In some embodiments of Formula XVII, B is



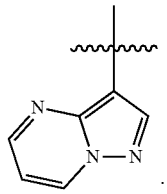
In some embodiments of Formula XVII, W^d is



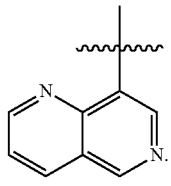
In some embodiments of Formula XVII, W^d is



In some embodiments of Formula XVII, W^d is

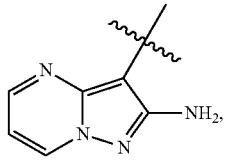


In some embodiments of Formula XVII, W^d is



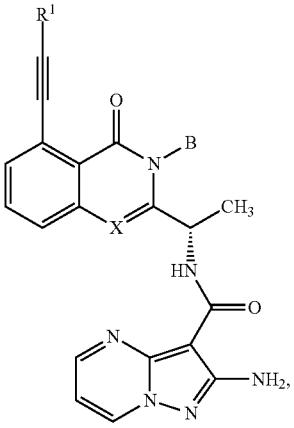
In some embodiments of Formula XVII, X is CH. In some embodiments, X is N.

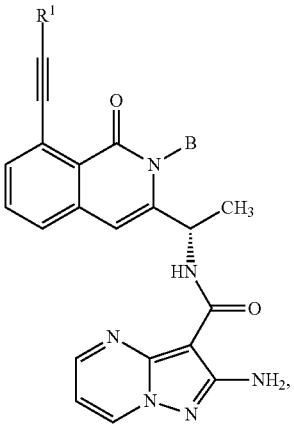
In some embodiments of Formula XVII, when X is CH, B is unsubstituted phenyl; W^d is

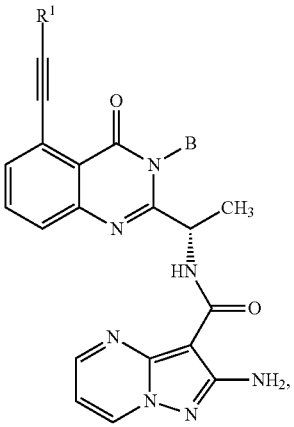


and R^1 is a linear alkyl, the linear alkyl contains at least four consecutively bonded carbons.

In some embodiments of Formula XVII, the compounds have the following formula:







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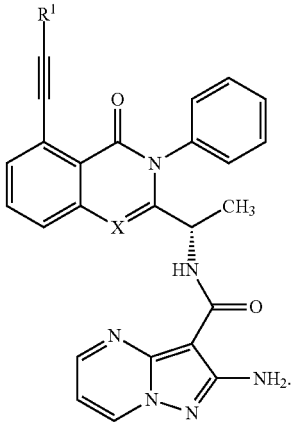

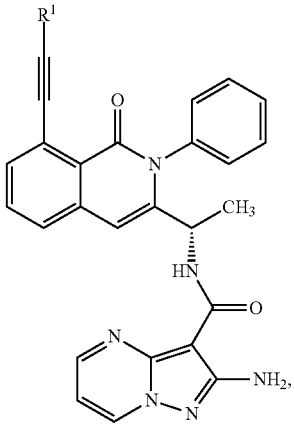

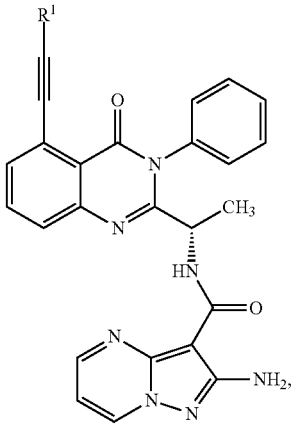

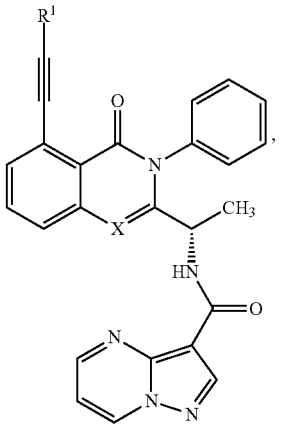

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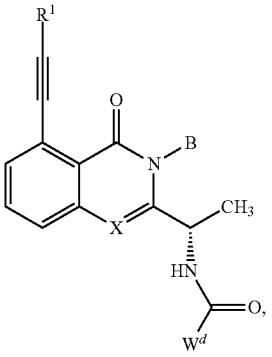

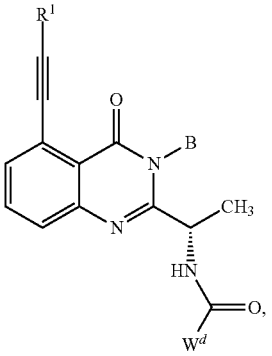

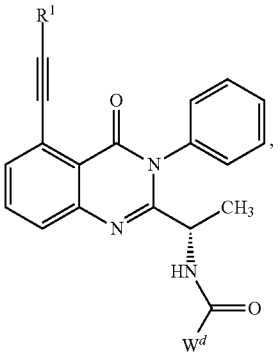

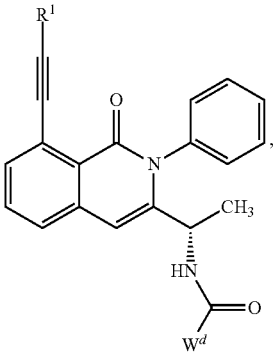

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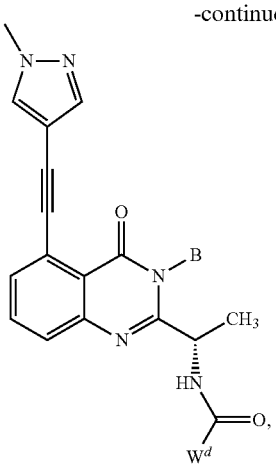

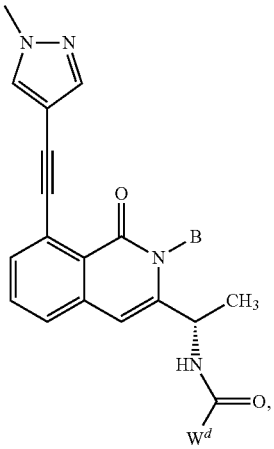

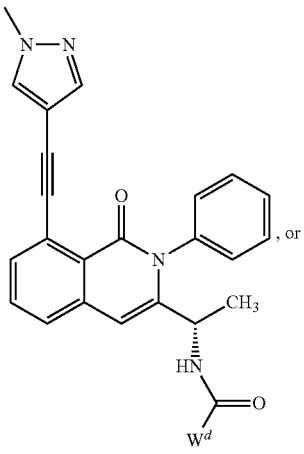

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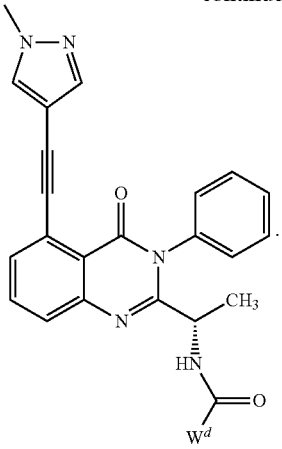
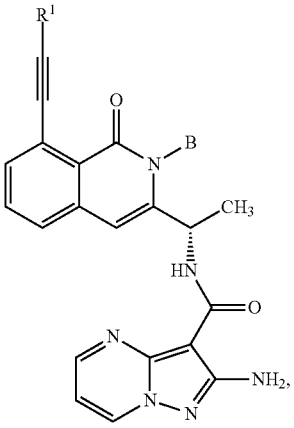
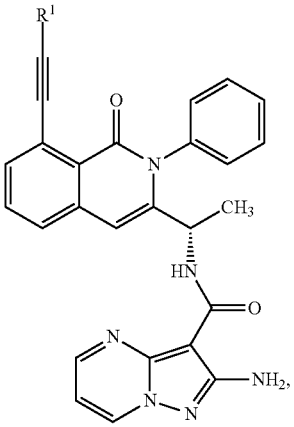


In some embodiments of Formula XVII, the compound has the following formula:





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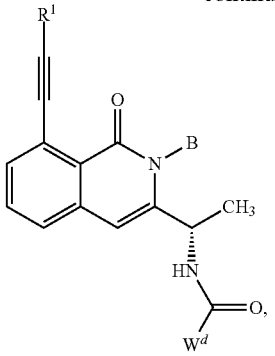
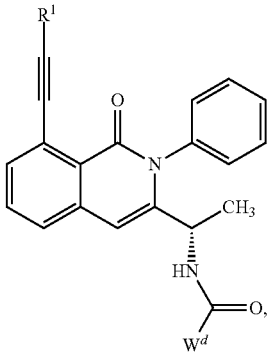
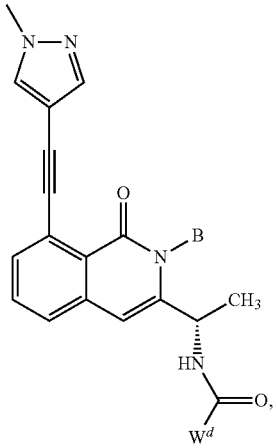
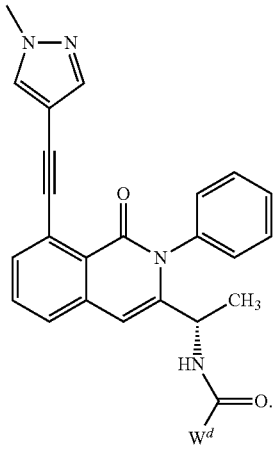






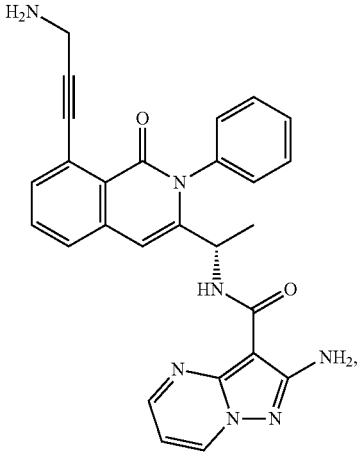


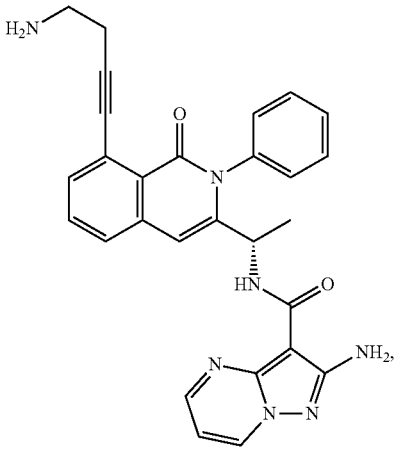
In certain embodiments, alkyl is C_1-C_8 alkyl. In certain embodiments, alkyl is C_1-C_6 alkyl. In another embodiment, alkyl is C_1-C_3 alkyl. In certain embodiments, alkenyl is C_2-C_8 alkenyl. In certain embodiments, alkenyl is C_2-C_6 alkenyl. In

another embodiment, alkenyl is C_2-C_3 alkenyl. In certain embodiments, alkynyl is C_2-C_8 alkynyl. In certain embodiments, alkynyl is C_2-C_6 alkynyl. In another embodiment, alkynyl is C_2-C_3 alkynyl.

In certain embodiments, cycloalkyl is C_3-C_8 cycloalkyl. In certain embodiments, cycloalkyl is C_3-C_6 cycloalkyl. In certain embodiments, cycloalkyl is C_3-C_4 cycloalkyl. In certain embodiments, heterocycloalkyl is a 3 to 14 membered saturated or partially saturated cycle containing one or more heteroatoms selected from a group consisting of N, O, and S. In certain embodiments, heterocycloalkyl is 3 to 10 membered. In another embodiment, heterocycloalkyl is 3 to 6 membered. In another embodiment, heterocycloalkyl is 6 membered. In certain embodiments, aryl is a C_6-C_{14} aromatic cycle. In certain embodiments, aryl is C_6-C_{10}. In another embodiment, aryl is C_6. In certain embodiments, heteroaryl is a 5 to 14 membered aromatic cycle containing one or more heteroatoms selected from a group consisting of N, O, and S. In certain embodiments, heteroaryl is 5 to 10 membered. In another embodiment, heteroaryl is 5 to 6 membered. In another embodiment, heteroaryl is 6 membered.

In certain embodiments, the compound provided herein is not a compound selected from:





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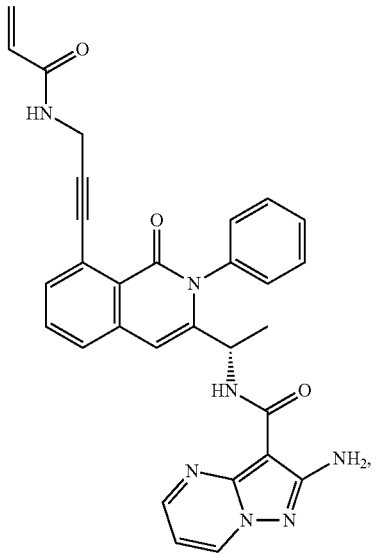

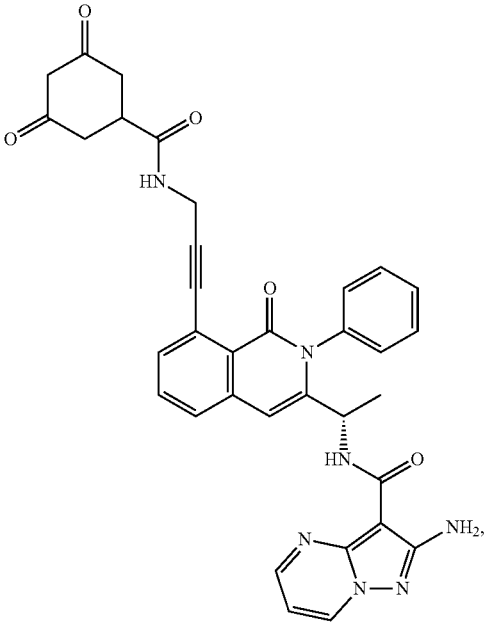

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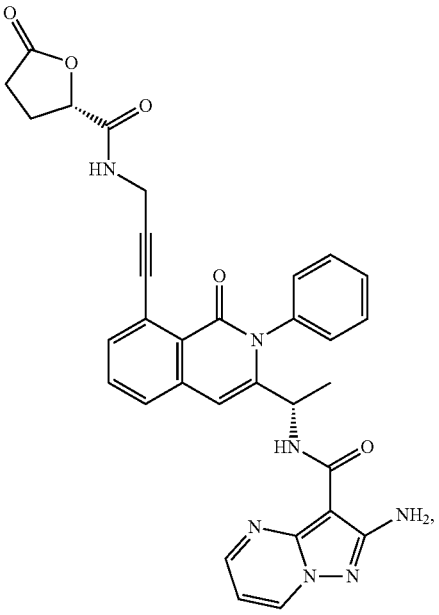

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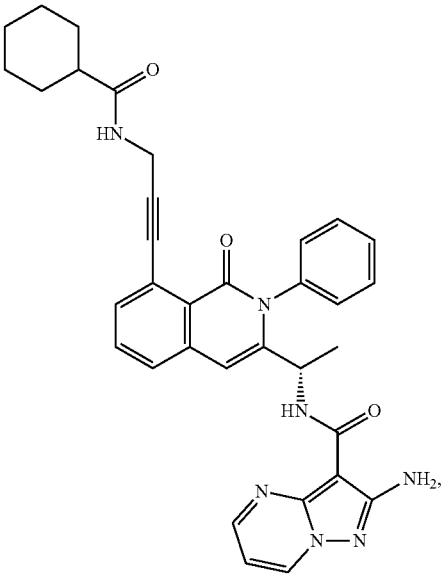

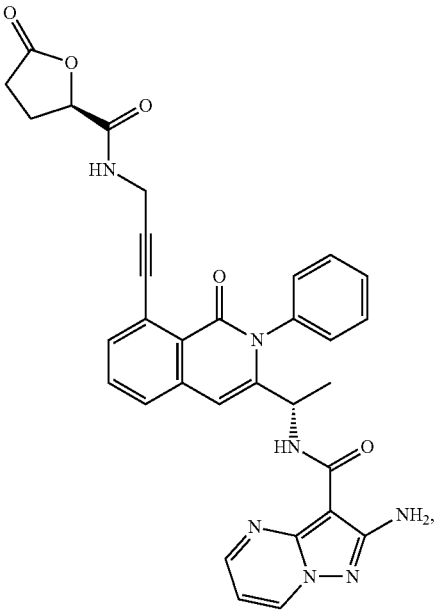

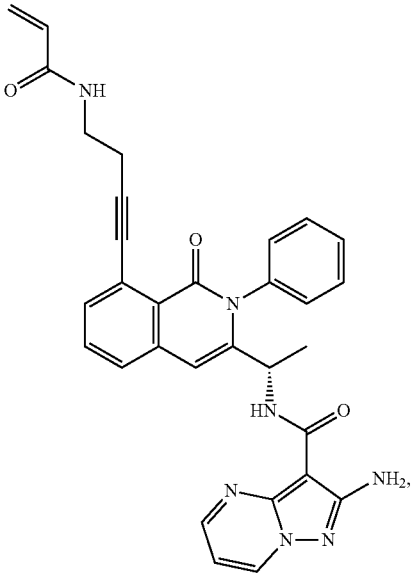

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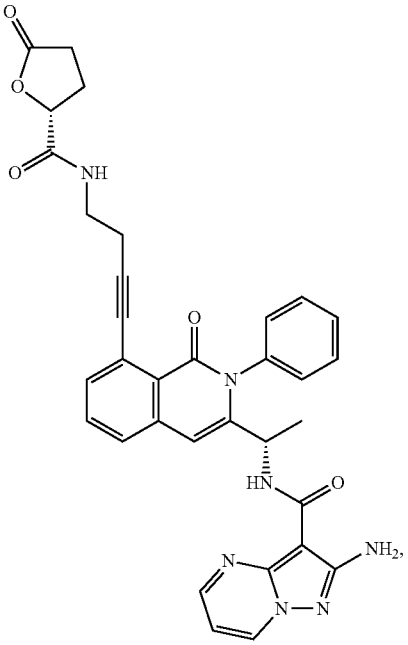

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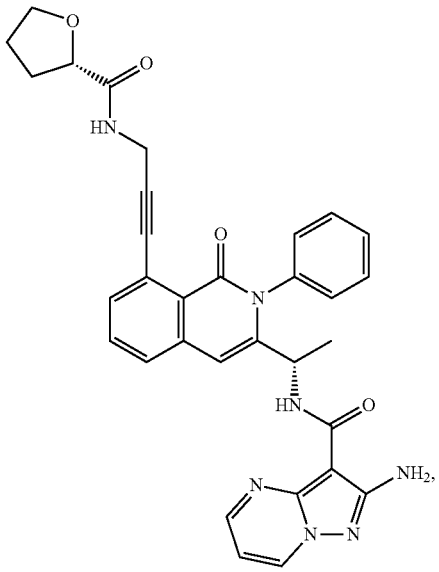

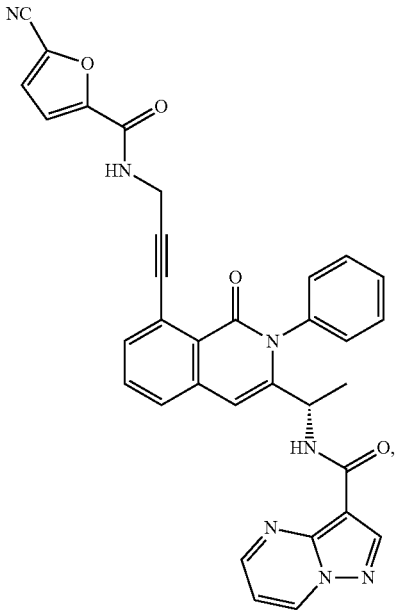

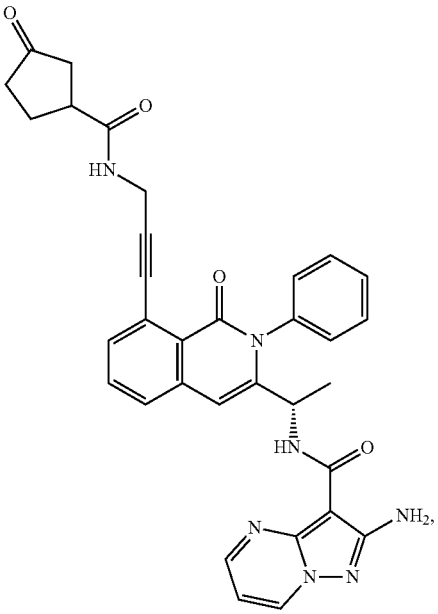

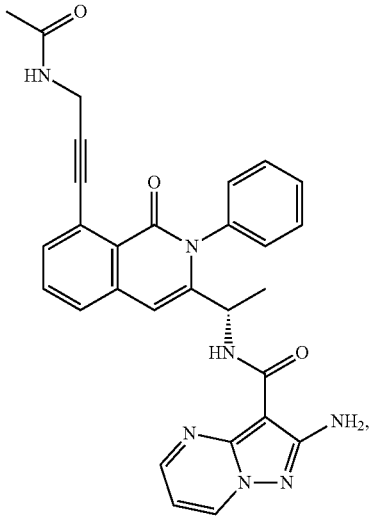

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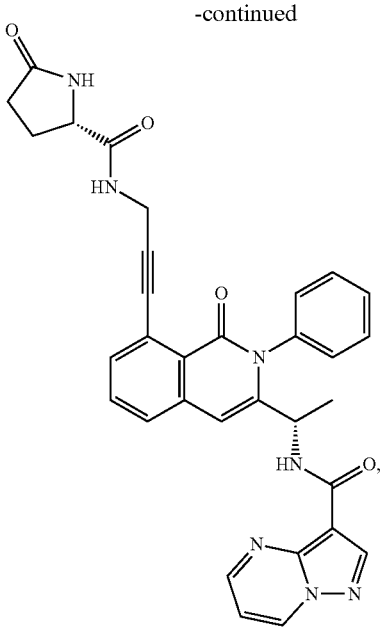

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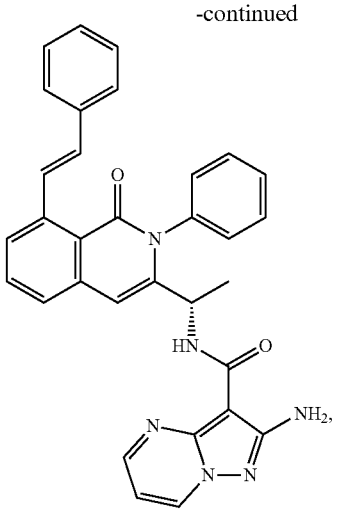

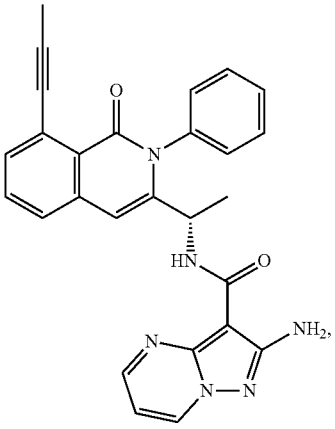

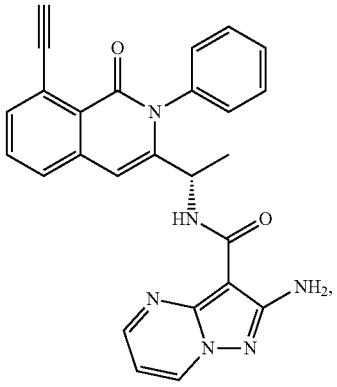

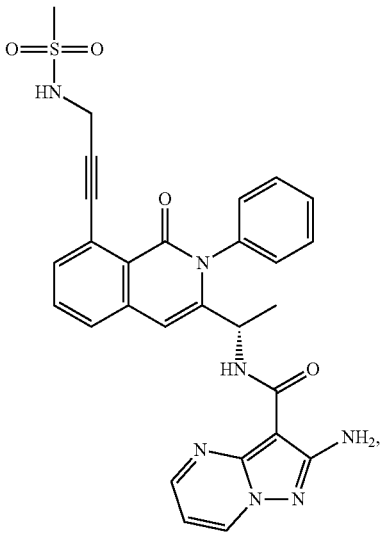

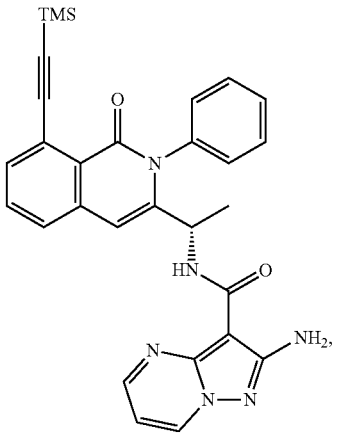

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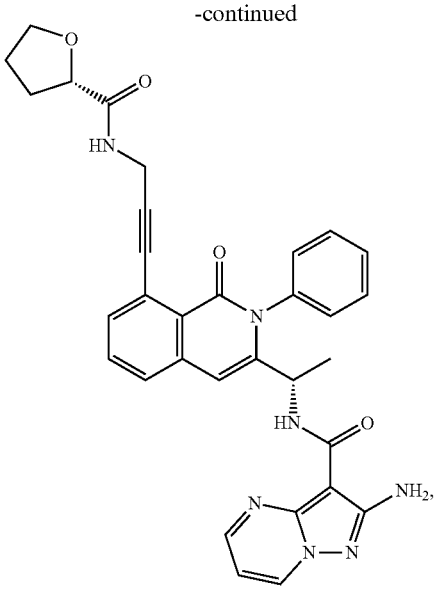
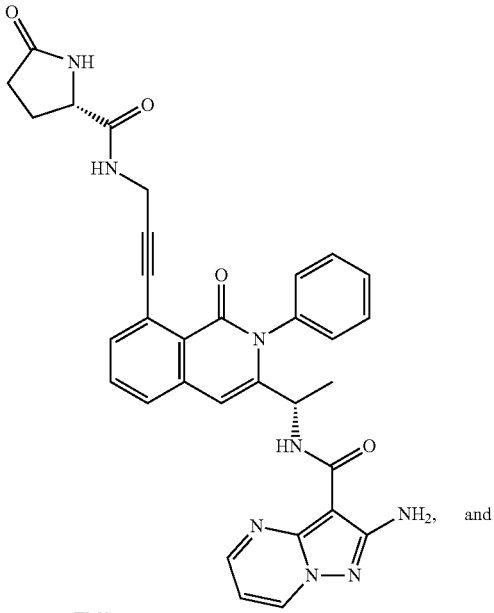
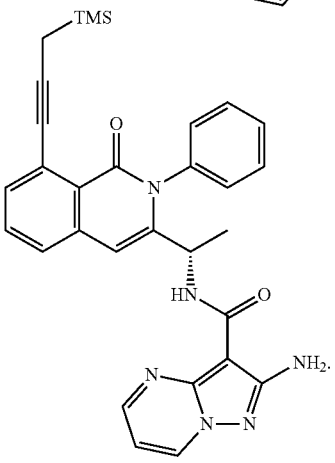




and



In certain embodiments, the compound of Formula (I"), (I'), (I), (A"), (A'), or (A) is in an (S)-stereochemical configuration.

In certain embodiments, the compound of Formula (I"), (I'), (I), (A"), (A'), or (A) is the S-enantiomer having an enantiomeric purity greater than 75%.

In certain embodiments, the compound of Formula (I') or (A') is a compound in Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, Table 9, Table 10, Table 11, Table 12, Table 13, or Table 14, or a pharmaceutically acceptable form thereof.

In certain embodiments, the compound of Formula (I') or (A') is a compound in Table 3, Table 4, Table 5, or Table 6 or a pharmaceutically acceptable form thereof.

In certain embodiments, the compound of Formula (I') or (A') is a compound in Table 3 or Table 4 or a pharmaceutically acceptable form thereof. In certain embodiments, the compound of Formula (I') or (A') is a compound in Table 3 or a pharmaceutically acceptable form thereof. In certain embodiments, the compound of Formula (I') or (A') is a compound in Table 5 or a pharmaceutically acceptable form thereof. In certain embodiments, the compound of Formula (I') or (A') is a compound in Table 7 or a pharmaceutically acceptable form thereof. In certain embodiments, the compound of Formula (I') or (A') is a compound in Table 9 or a pharmaceutically acceptable form thereof. In certain embodiments, the compound of Formula (I') or (A') is a compound in Table 11 or a pharmaceutically acceptable form thereof. In certain embodiments, the compound of Formula (I') or (A') is a compound in Table 13 or a pharmaceutically acceptable form thereof. In certain embodiments, the compound of Formula (I') or (A') is a compound in Table 4 or a pharmaceutically acceptable form thereof. In certain embodiments, the compound of Formula (I') or (A') is a compound in Table 6 or a pharmaceutically acceptable form thereof. In certain embodiments, the compound of Formula (I') or (A') is a compound in Table 8 or a pharmaceutically acceptable form thereof. In certain embodiments, the compound of Formula (I') or (A') is a compound in Table 10 or a pharmaceutically acceptable form thereof. In certain embodiments, the compound of Formula (I') or (A') is a compound in Table 12 or a pharmaceutically acceptable form thereof. In certain embodiments, the compound of Formula (I') or (A') is a compound in Table 14 or a pharmaceutically acceptable form thereof.

TABLE 3

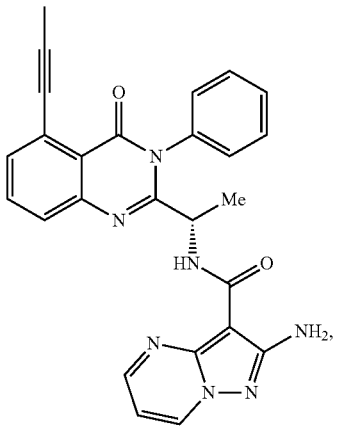
Compound 1	

TABLE 3-continued

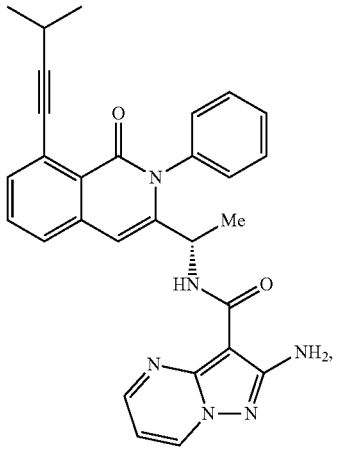
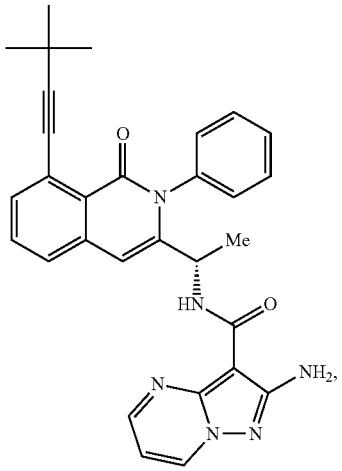
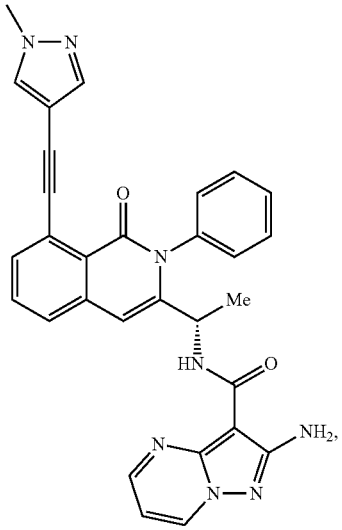
Compound 2	
Compound 3	
Compound 4	

TABLE 3-continued

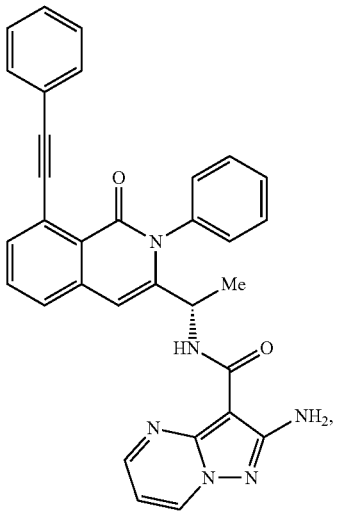
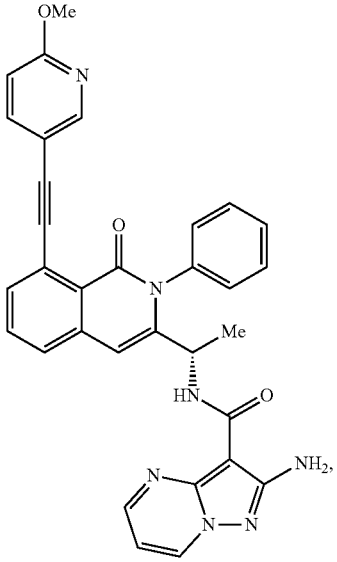
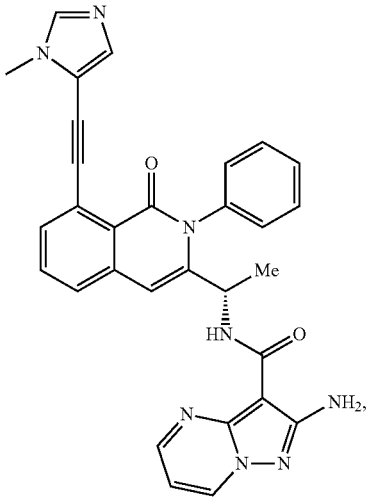
Compound 5	
Compound 6	
Compound 7	

TABLE 3-continued

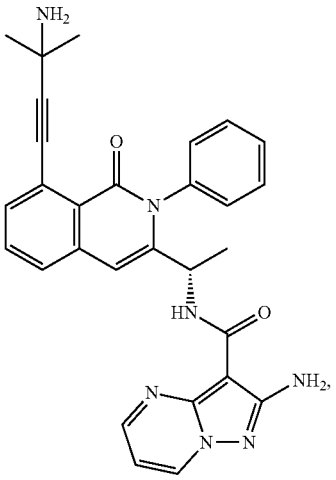
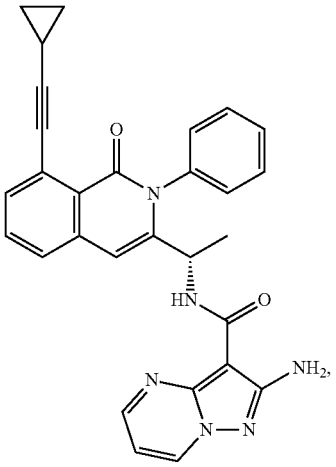
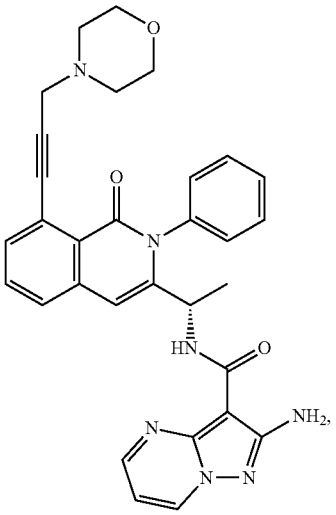
Compound 8	
Compound 9	
Compound 10	

TABLE 3-continued

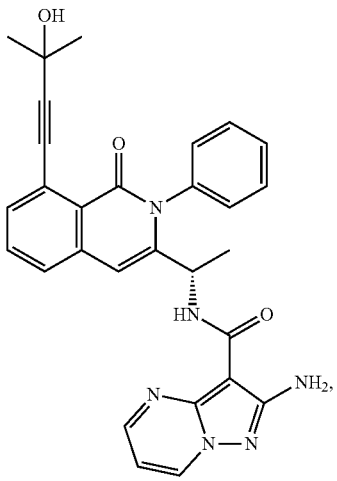
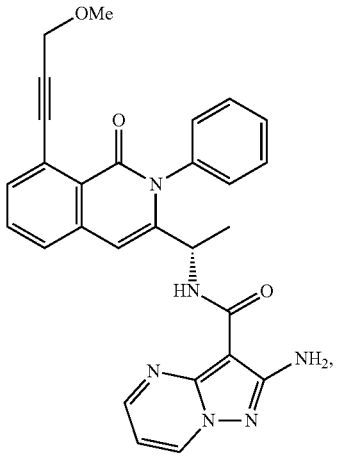
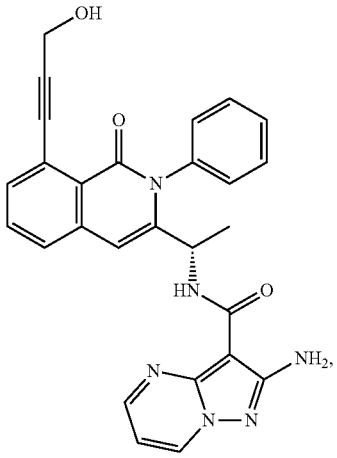
Compound 11	
Compound 12	
Compound 13	

TABLE 3-continued

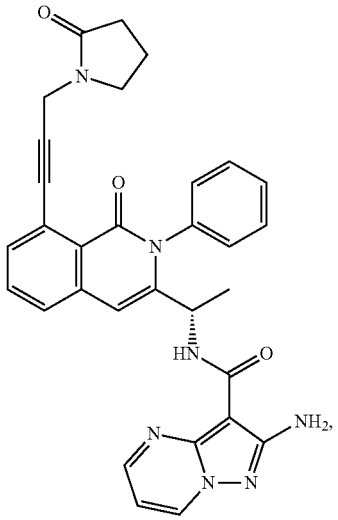
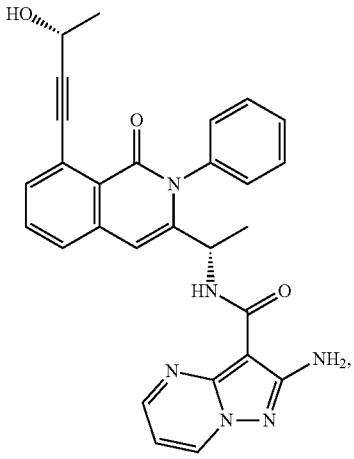
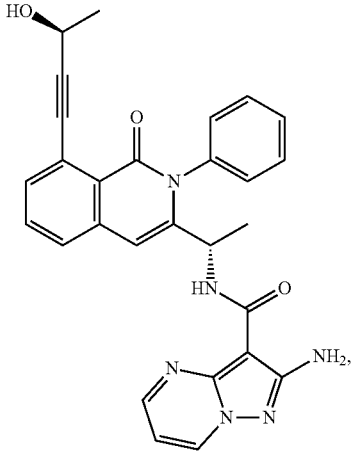
Compound 14	
Compound 15	
Compound 16	

TABLE 3-continued

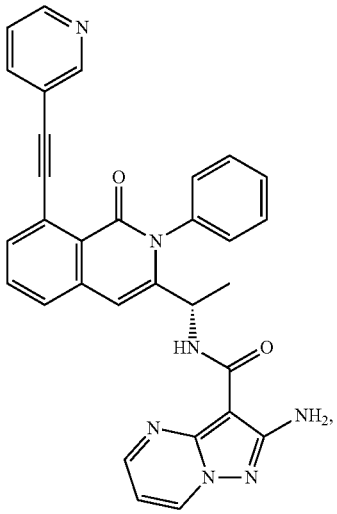
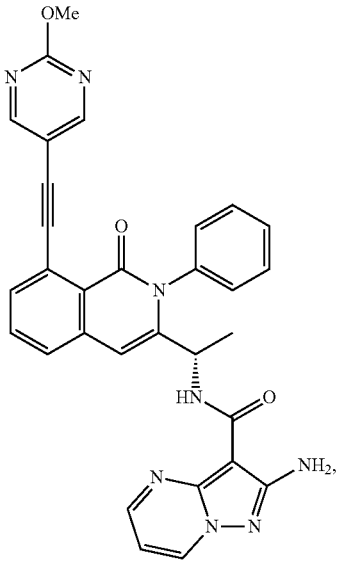
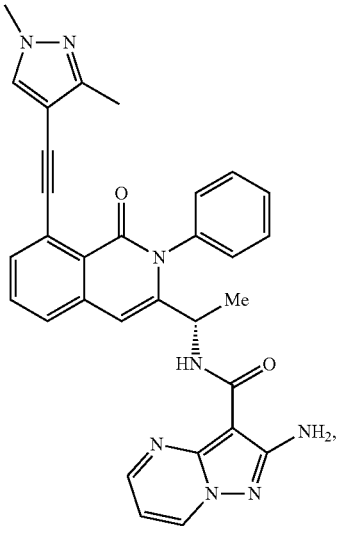
Compound 17	
Compound 18	
Compound 19	

TABLE 3-continued

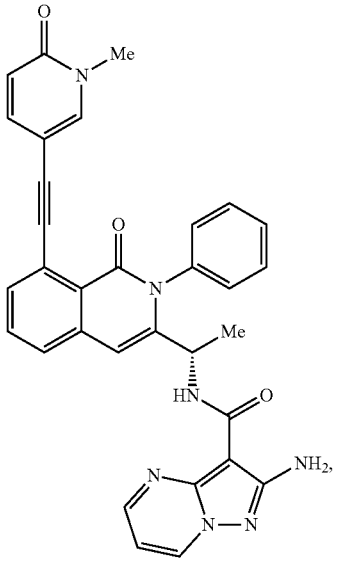
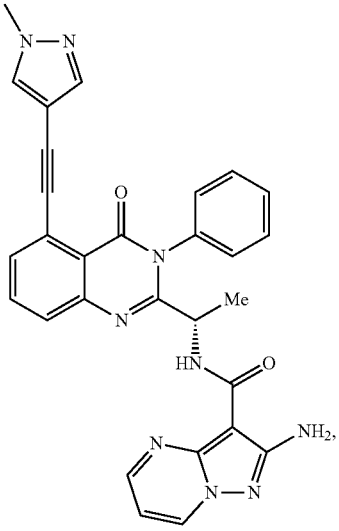
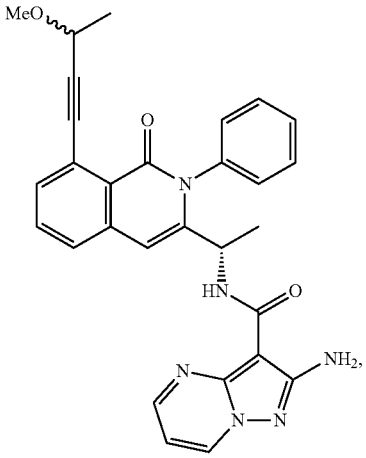
Compound 20	
Compound 21	
Compound 22	

TABLE 3-continued

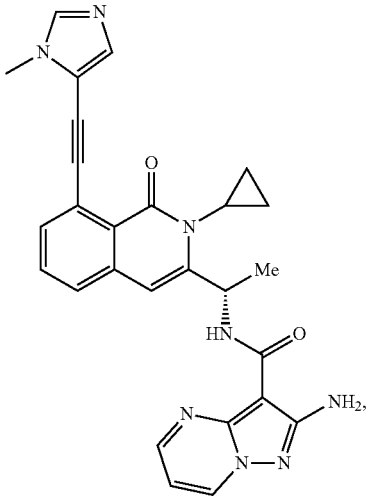
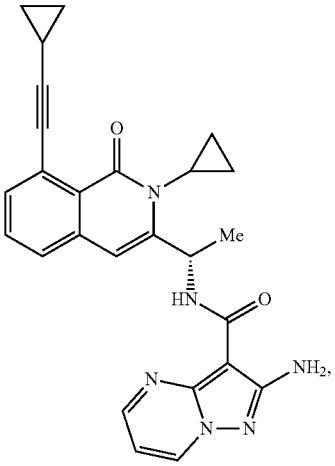
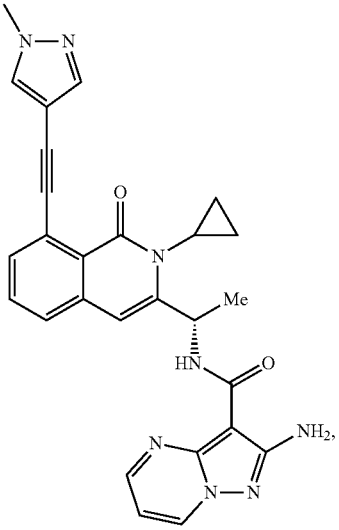
Compound 23	
Compound 24	
Compound 25	

TABLE 3-continued

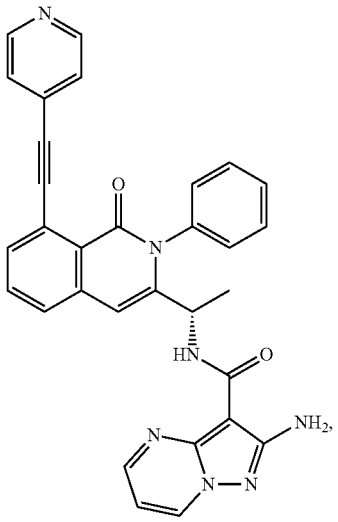
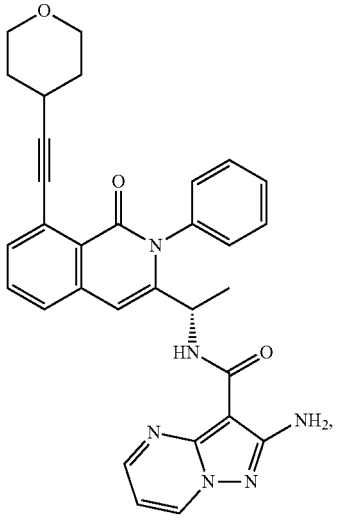
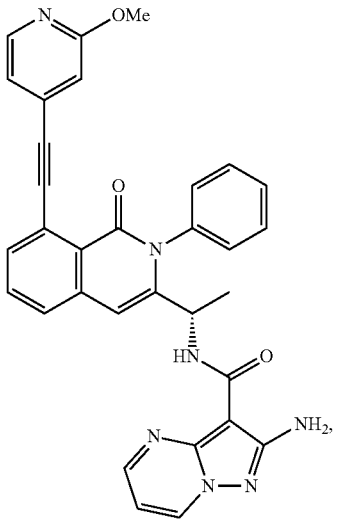
Compound 26	
Compound 27	
Compound 28	

TABLE 3-continued

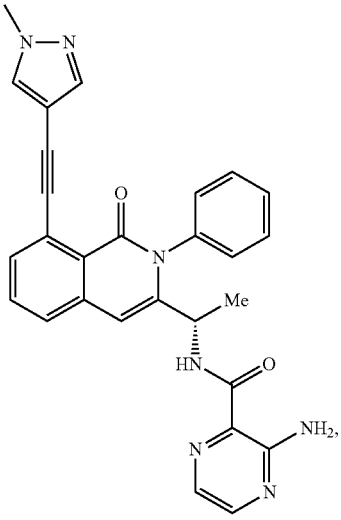
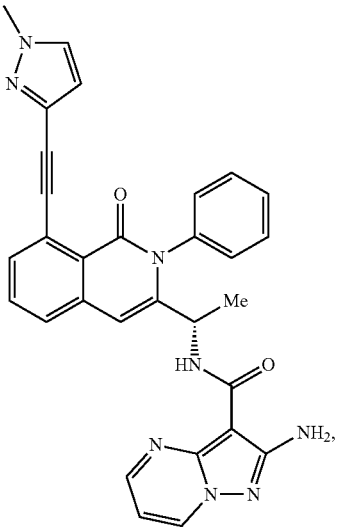
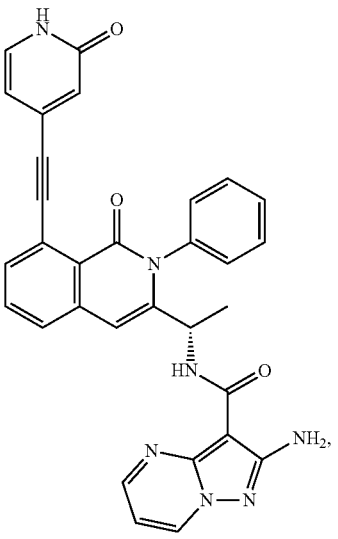
Compound 29	
Compound 30	
Compound 31	

TABLE 3-continued

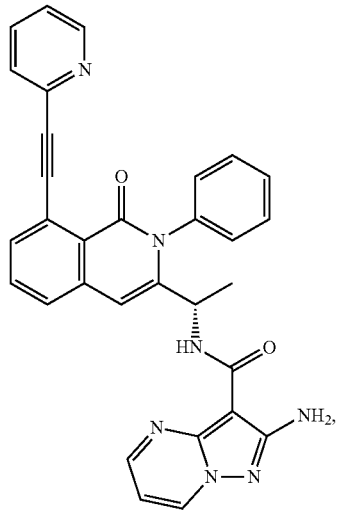
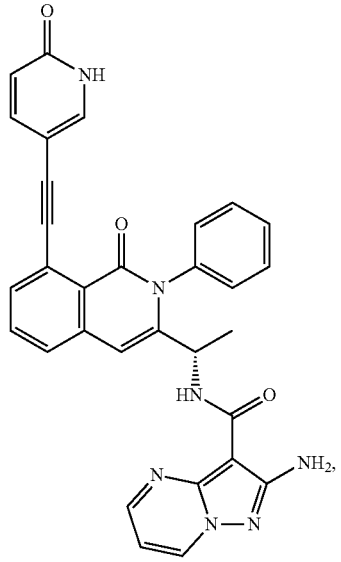
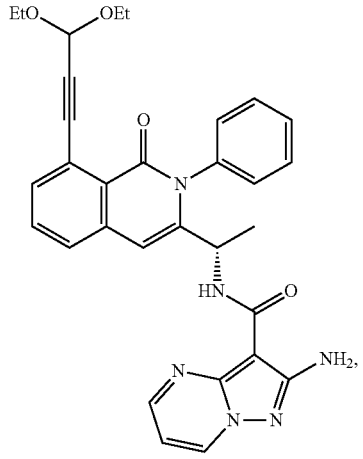
Compound 32	
Compound 33	
Compound 34	

TABLE 3-continued

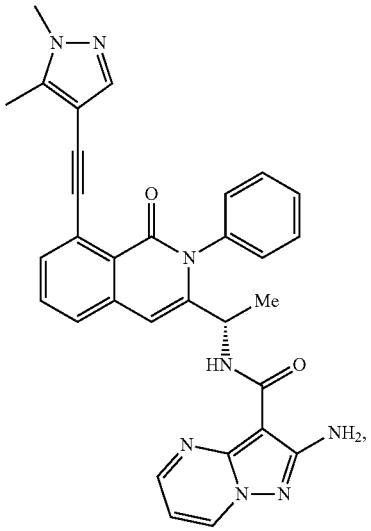
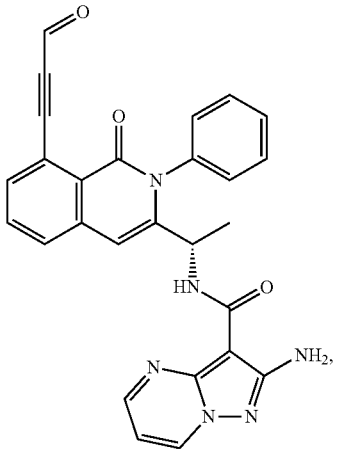
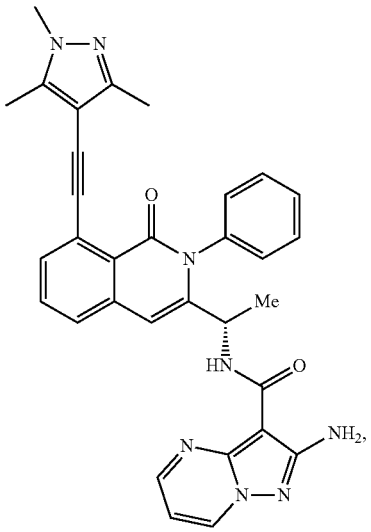
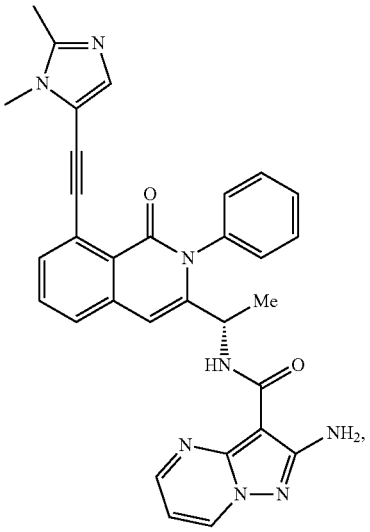
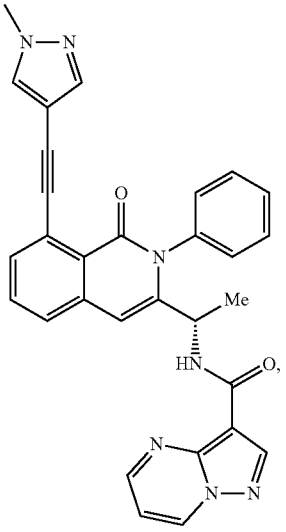
Compound 35	
Compound 36	
Compound 37	

TABLE 3-continued

Compound 38



Compound 39



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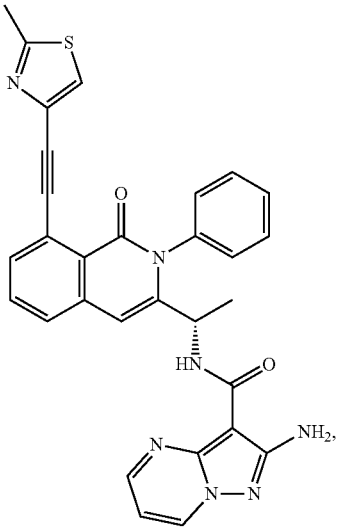
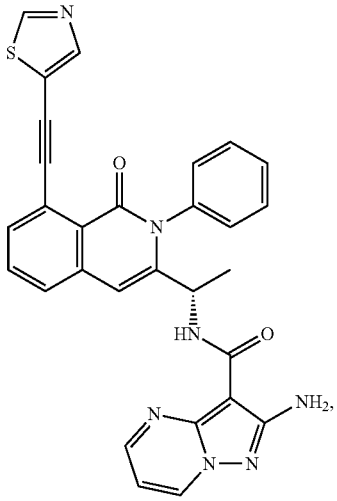
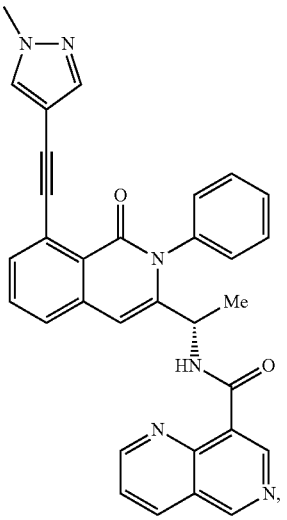


TABLE 3-continued

Compound 41



Compound 42



Compound 43

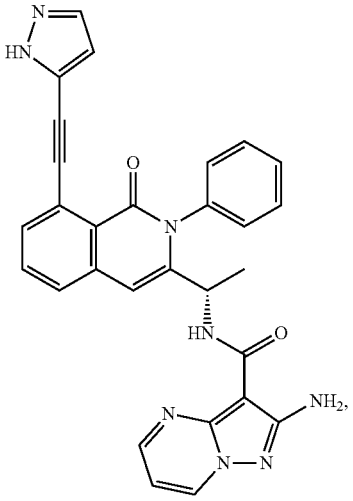


TABLE 3-continued

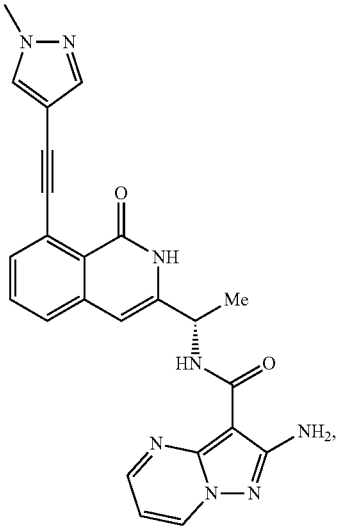
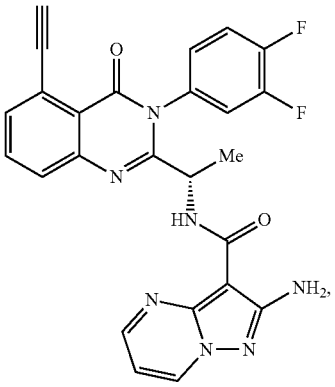
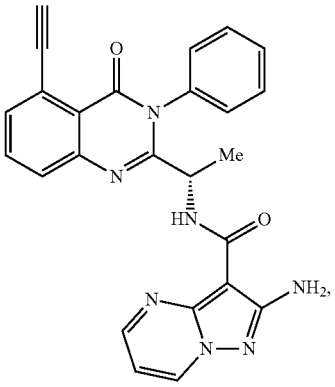
Compound 44	
Compound 45	
Compound 46	

TABLE 3-continued

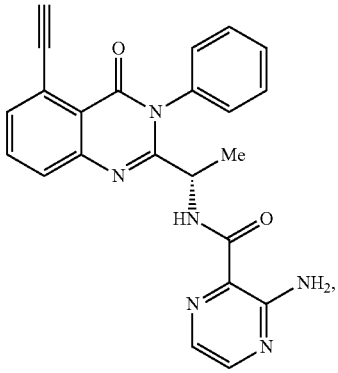
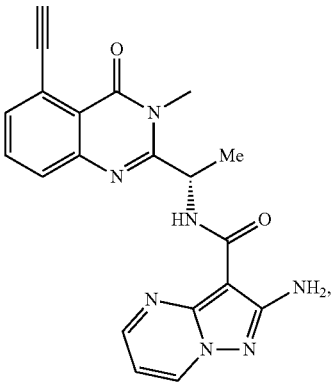
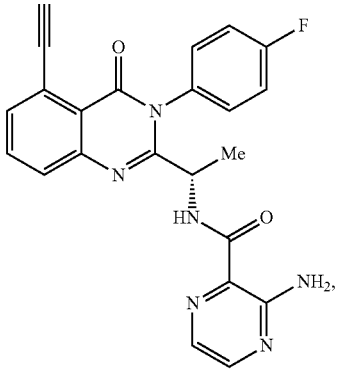
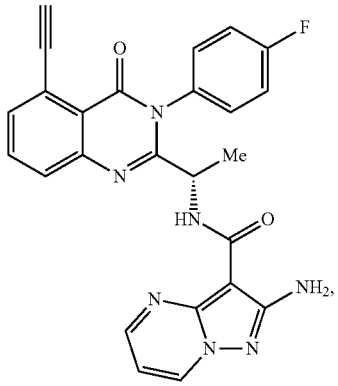
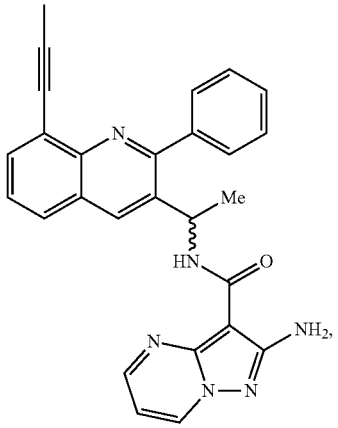
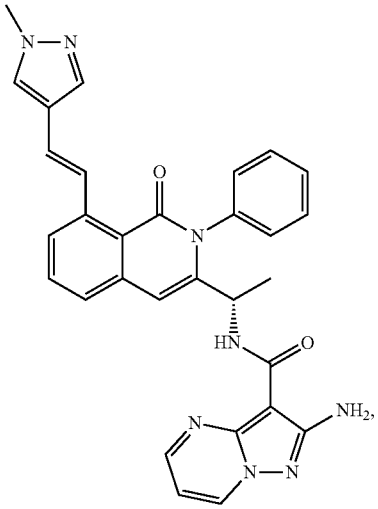
Compound 47	
Compound 48	
Compound 49	
Compound 50	

TABLE 3-continued

Compound 51



Compound 52



Compound 53

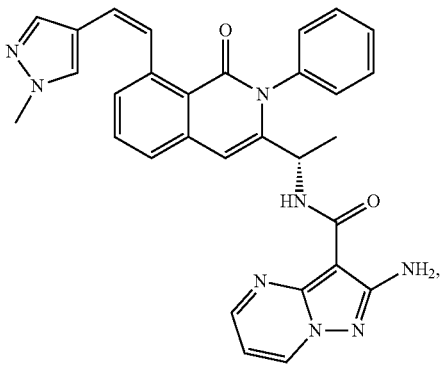
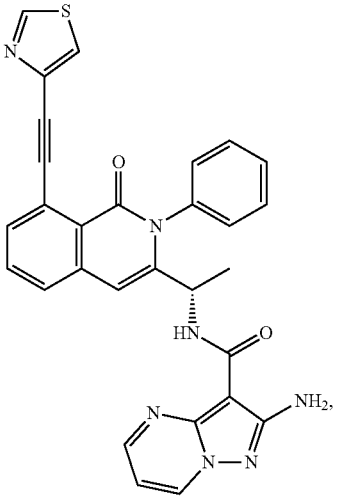
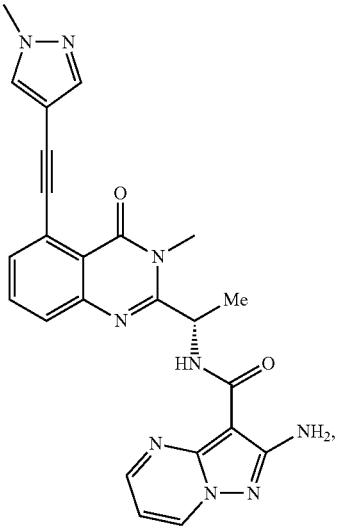


TABLE 3-continued

Compound 54



Compound 55



Compound 56

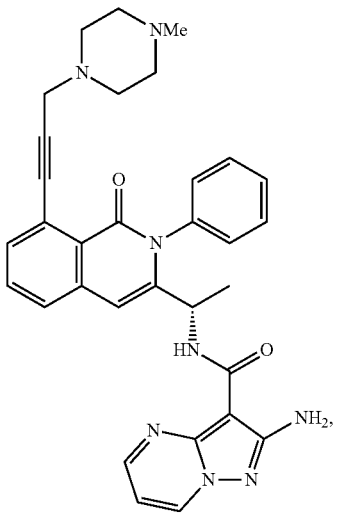


TABLE 3-continued

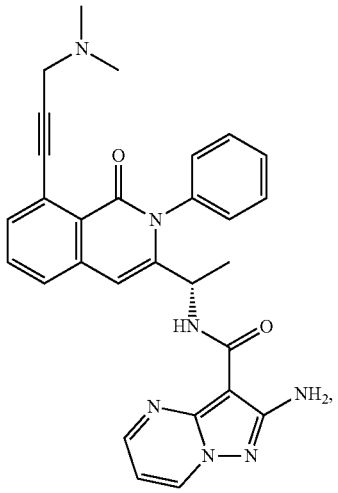
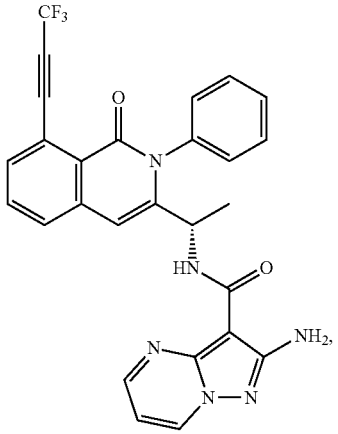
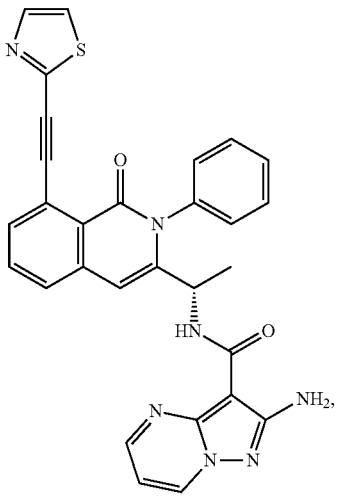
Compound 57	
Compound 58	
Compound 59	

TABLE 3-continued

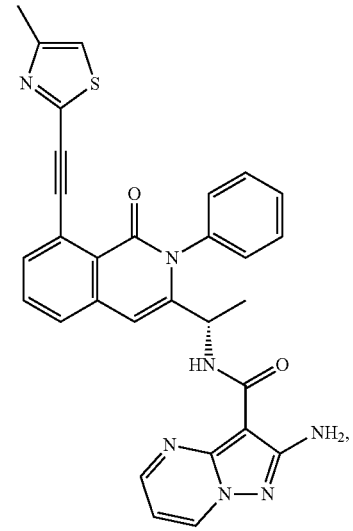
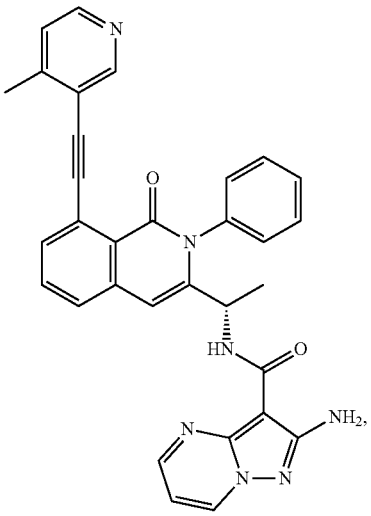
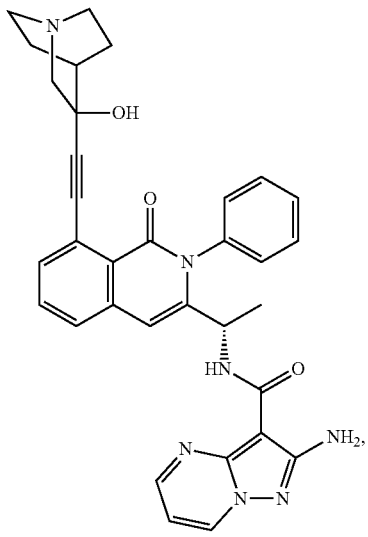
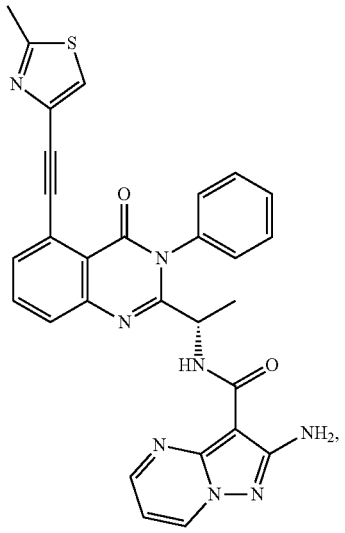
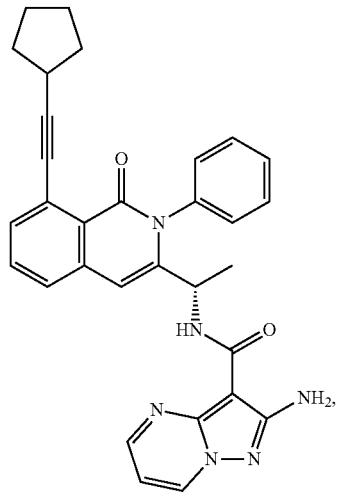
Compound 60	
Compound 61	
Compound 62	

TABLE 3-continued

Compound 63



Compound 64



Compound 65

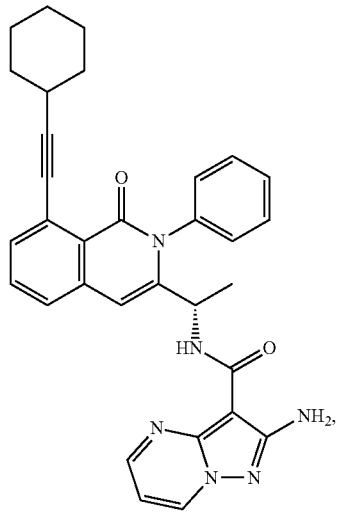
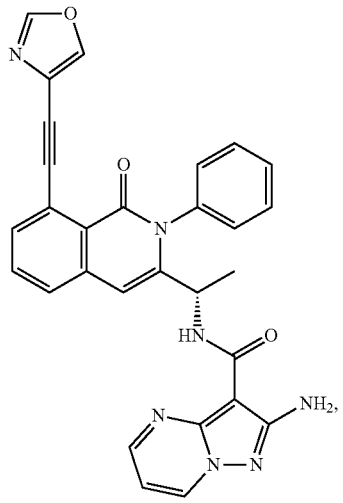
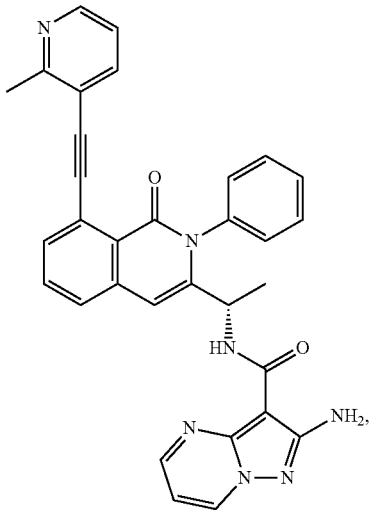


TABLE 3-continued

Compound 66



Compound 67



Compound 68

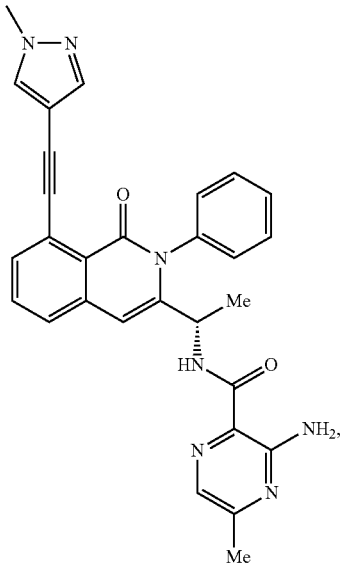
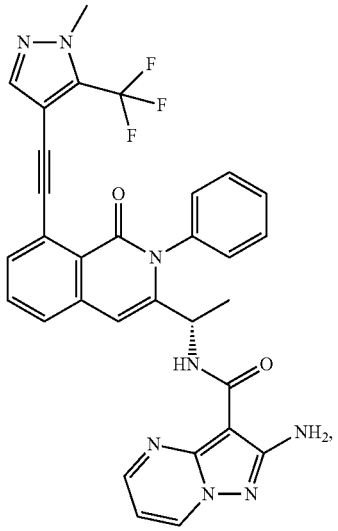
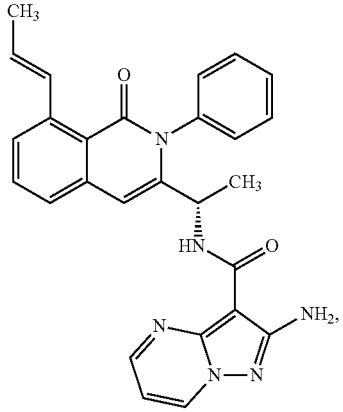


TABLE 3-continued

Compound 69



Compound 70



Compound 71

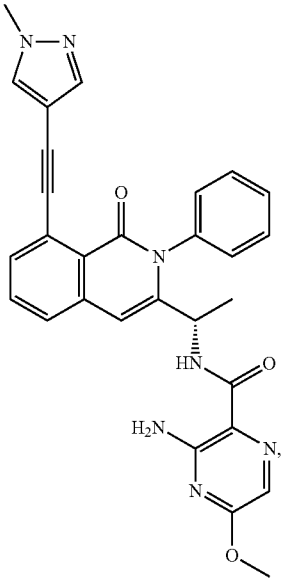
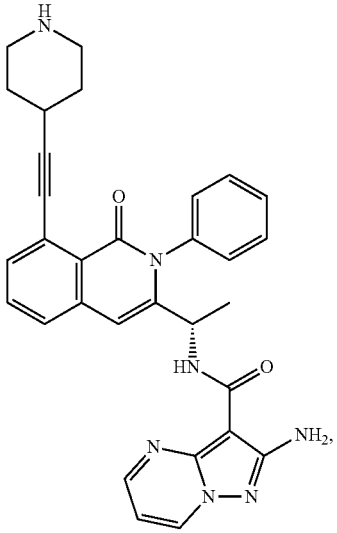
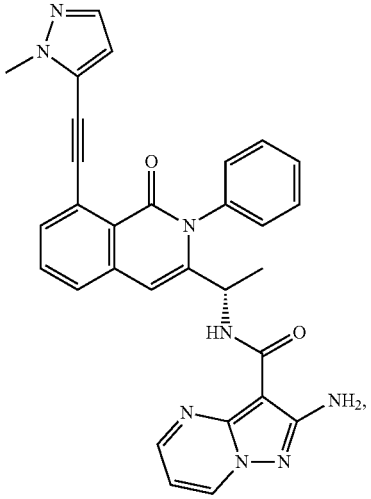


TABLE 3-continued

Compound 72



Compound 73



Compound 74

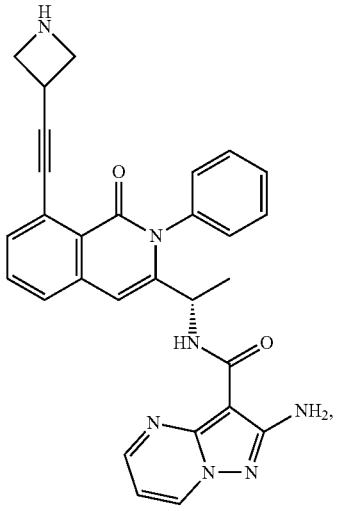


TABLE 3-continued

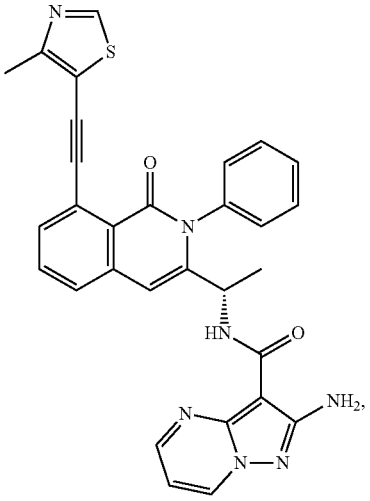
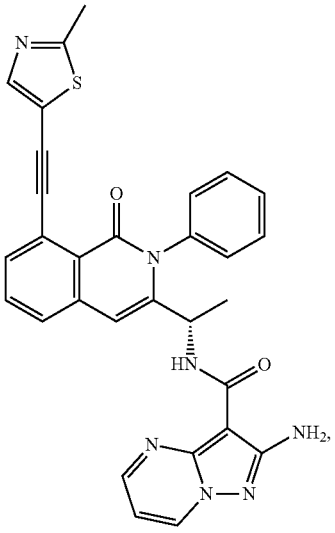
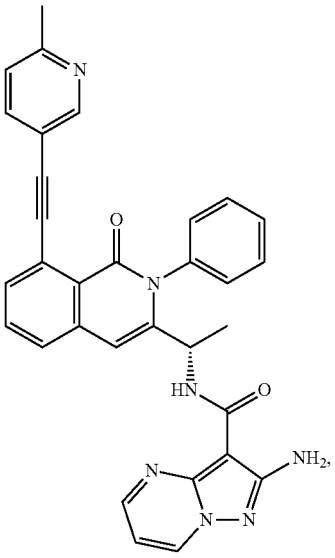
Compound 75	
Compound 76	
Compound 77	

TABLE 3-continued

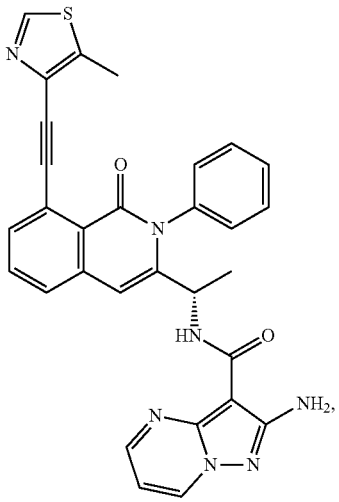
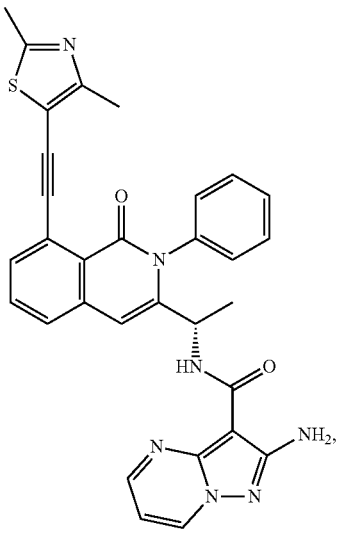
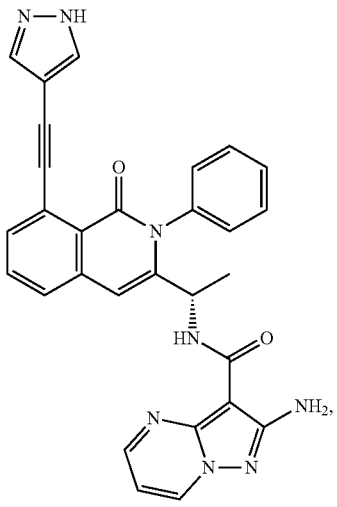
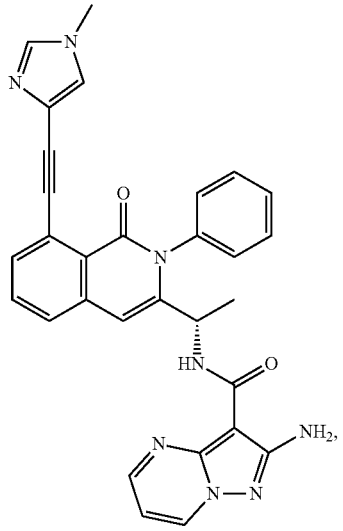
Compound 78	
Compound 79	
Compound 80	

TABLE 3-continued

Compound 81



Compound 82

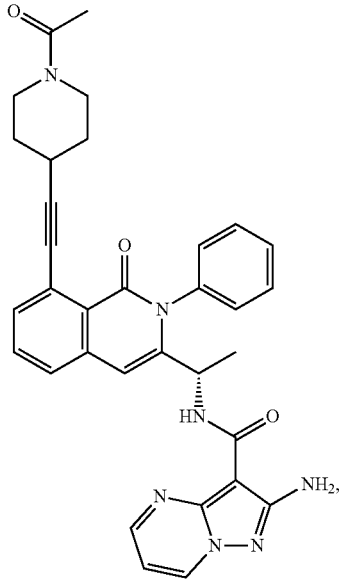
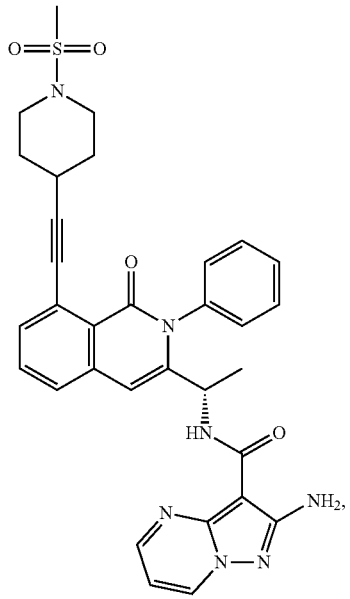
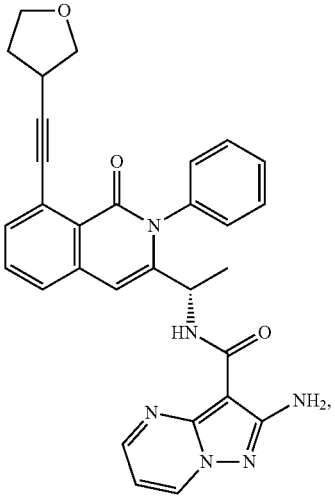


TABLE 3-continued

Compound 83



Compound 84



Compound 85

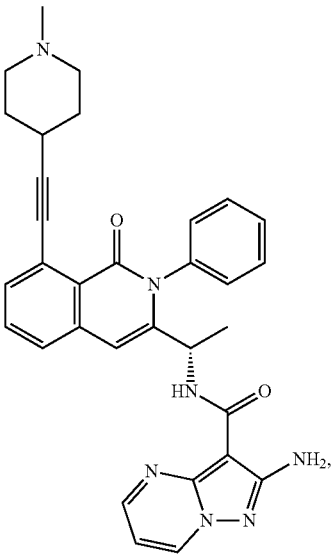


TABLE 3-continued

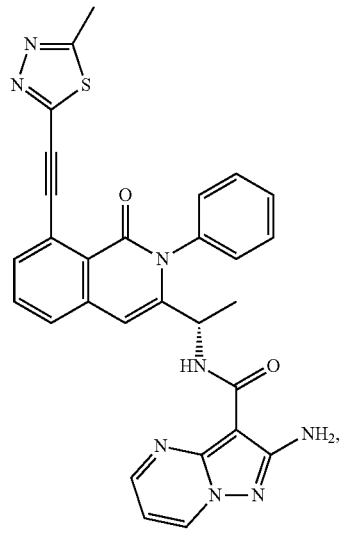
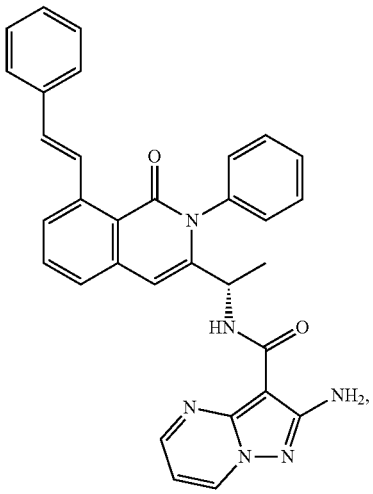
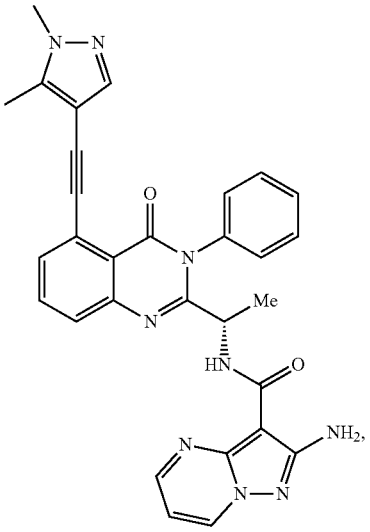
Compound 86	
Compound 87	
Compound 88	

TABLE 3-continued

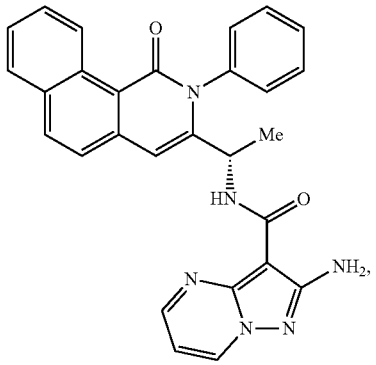
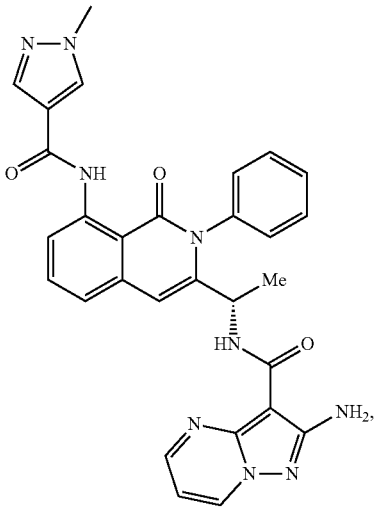
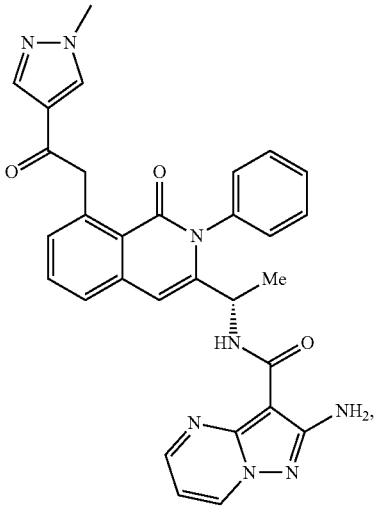
Compound 89	
Compound 90	
Compound 91	

TABLE 3-continued

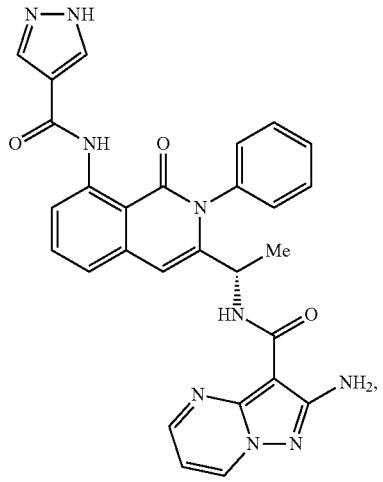
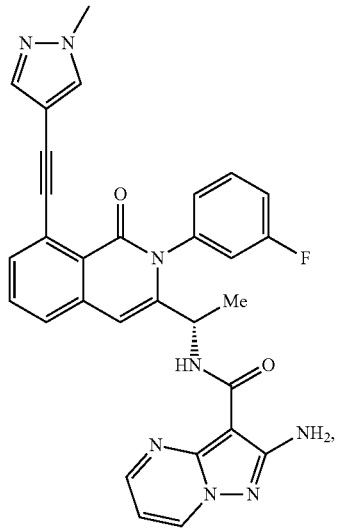
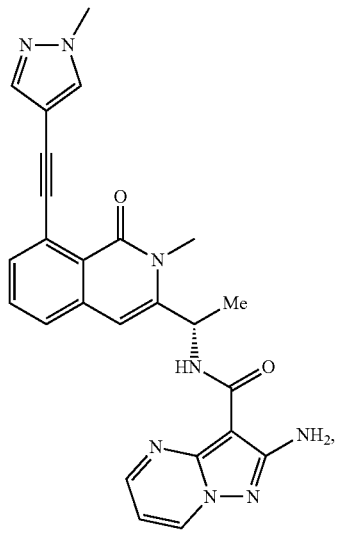
Compound 92	
Compound 93	
Compound 94	

TABLE 3-continued

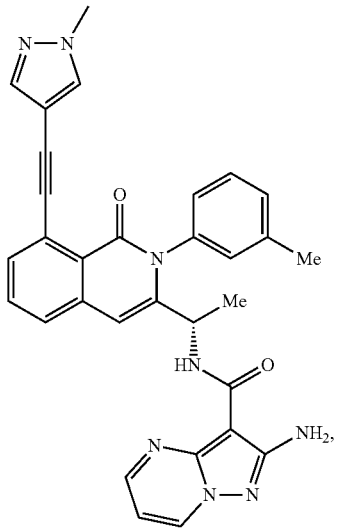
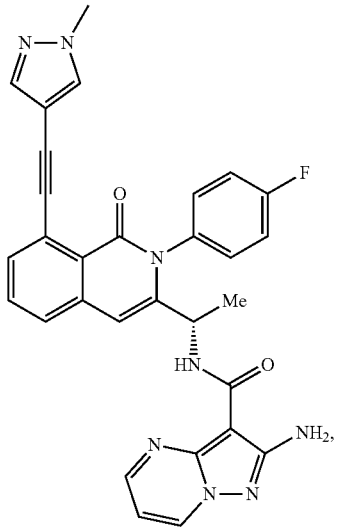
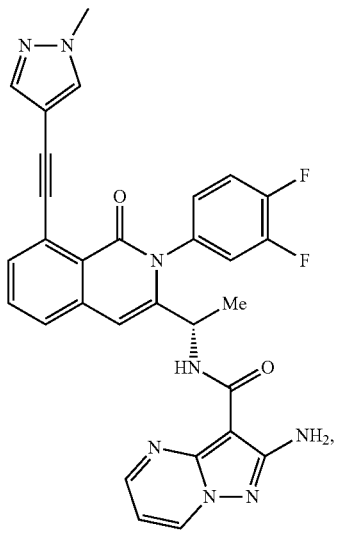
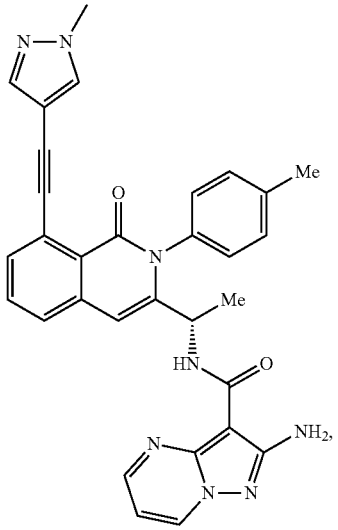
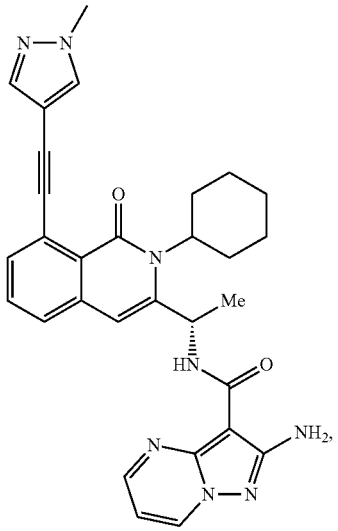
Compound 95	
Compound 96	
Compound 97	

TABLE 3-continued

Compound 98



Compound 99



Compound 100

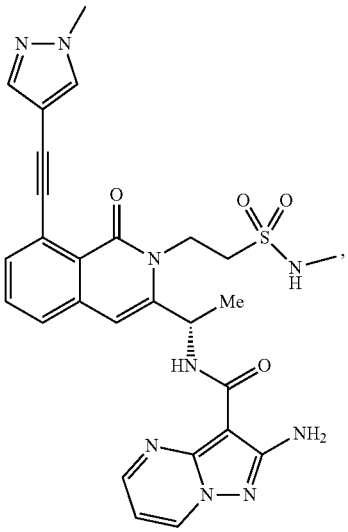
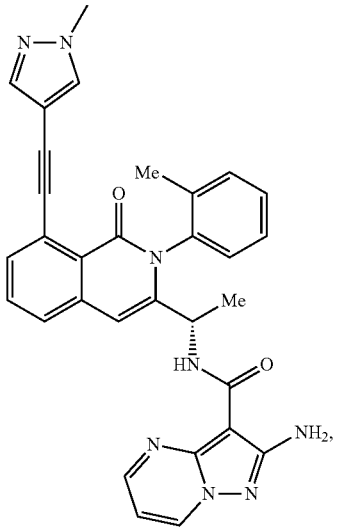
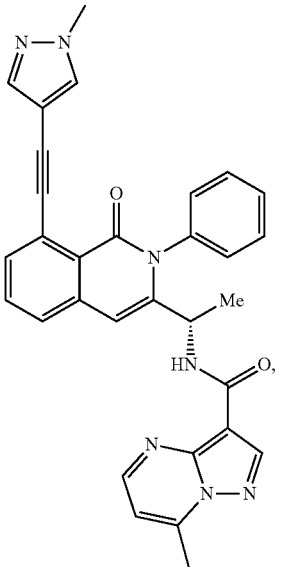


TABLE 3-continued

Compound 101



Compound 102



Compound 103

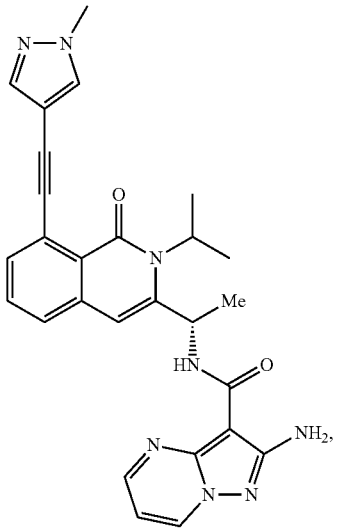
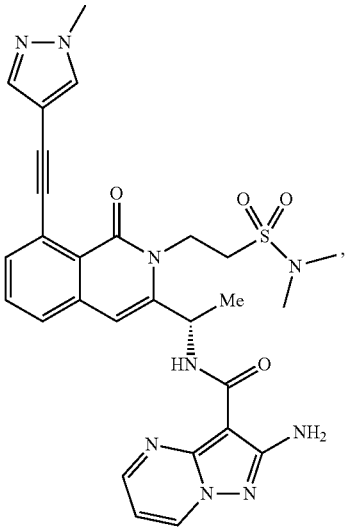
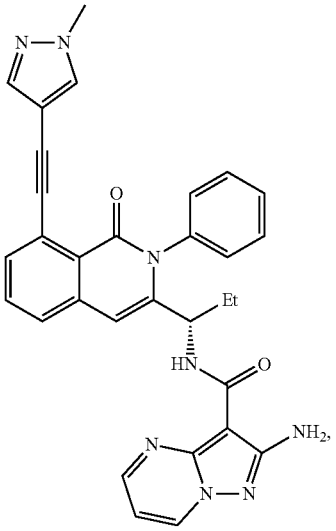


TABLE 3-continued

Compound 104



Compound 105



Compound 106

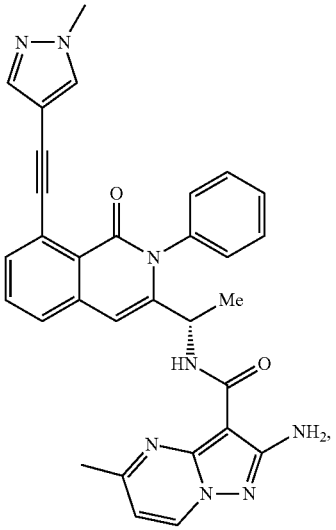
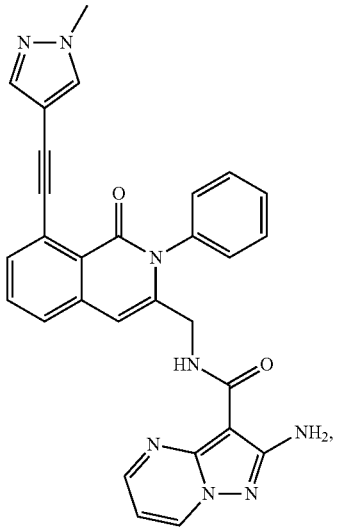
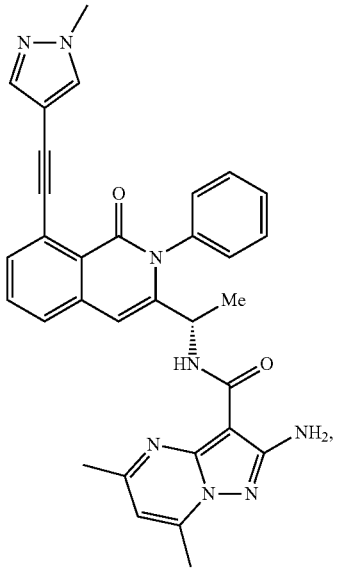


TABLE 3-continued

Compound 107



Compound 108



Compound 109

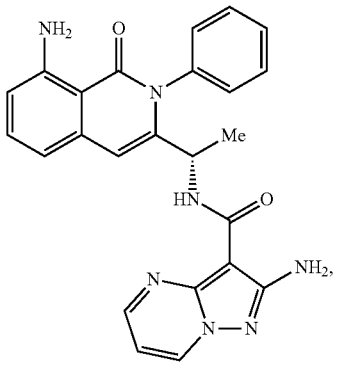
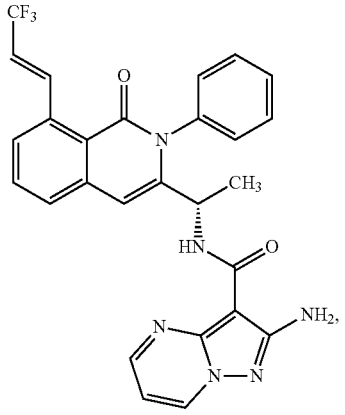
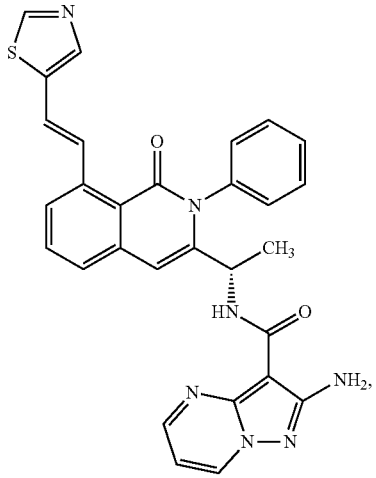


TABLE 4

Compound 1001



Compound 1002



Compound 1003

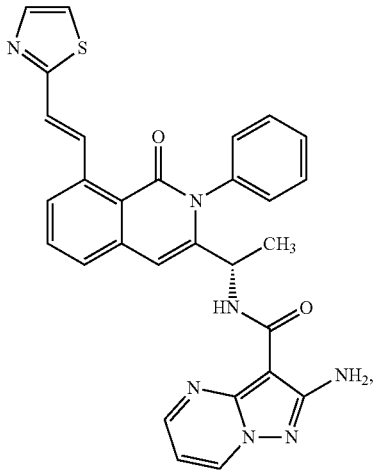
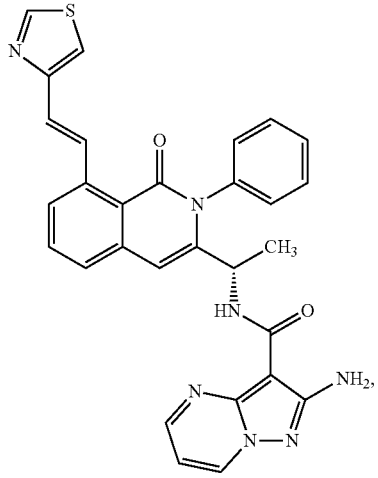
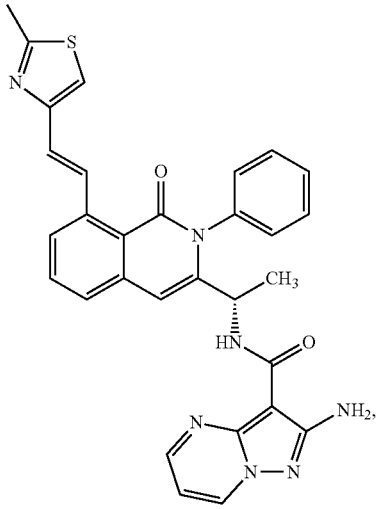


TABLE 4-continued

Compound 1004



Compound 1005



Compound 1006

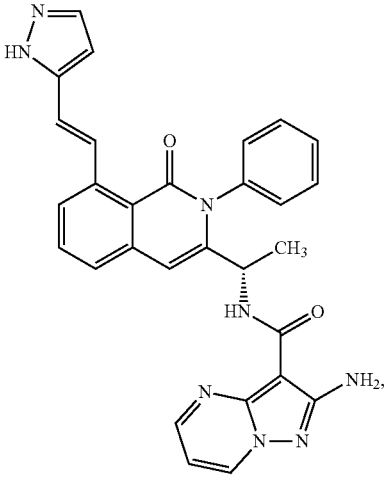
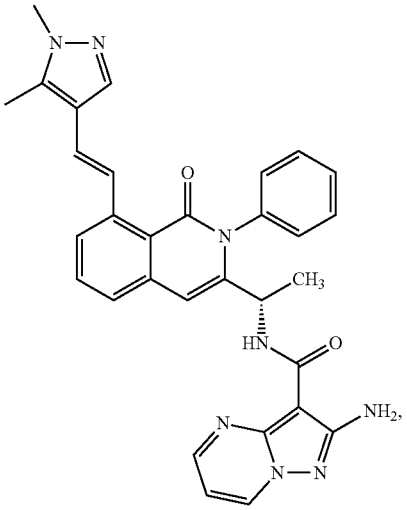
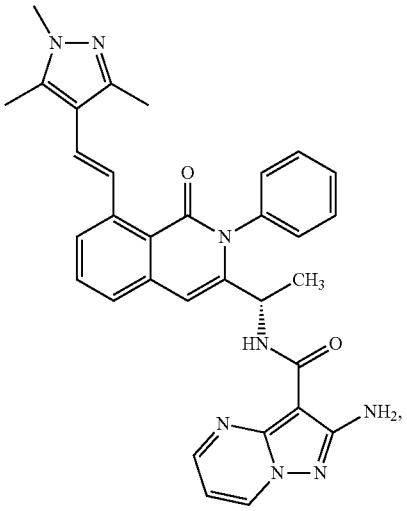


TABLE 4-continued

Compound 1007



Compound 1008



Compound 1009

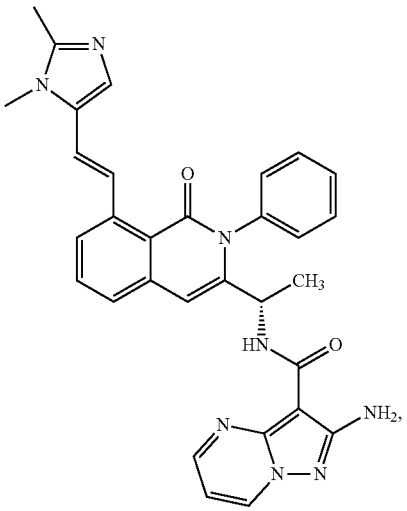
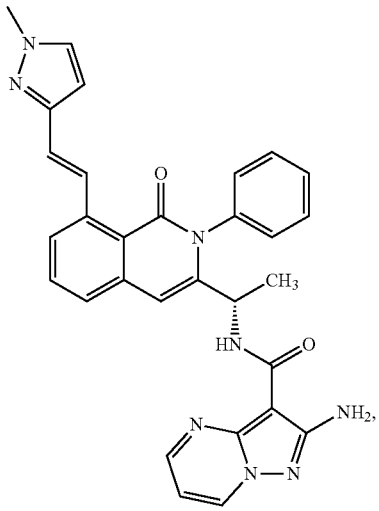
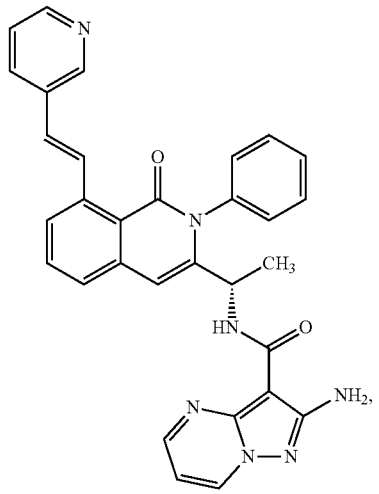


TABLE 4-continued

Compound 1010



Compound 1011



Compound 1012

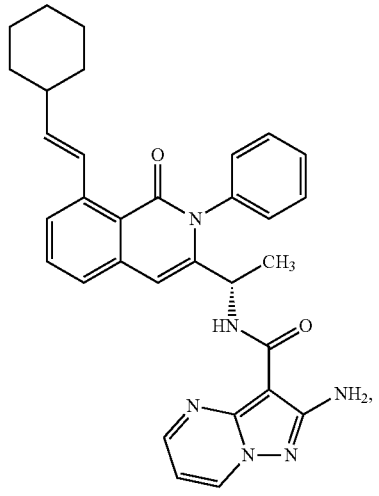


TABLE 4-continued

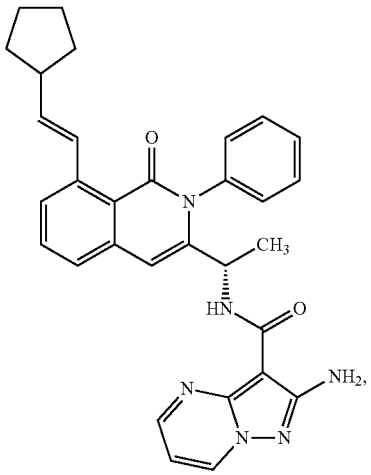
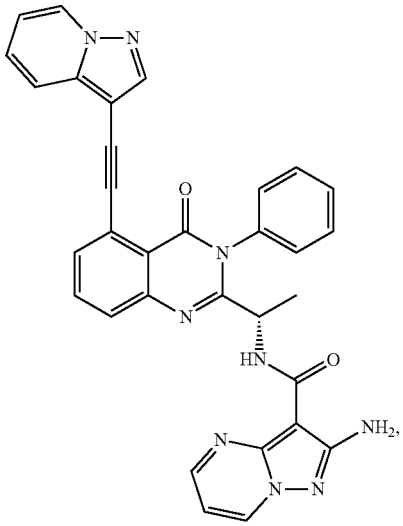
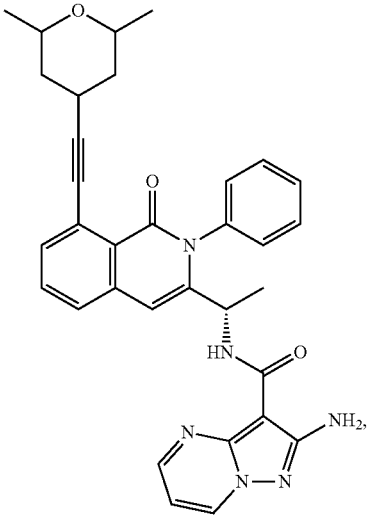
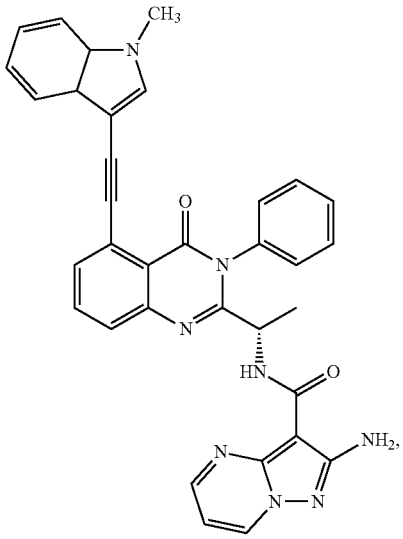
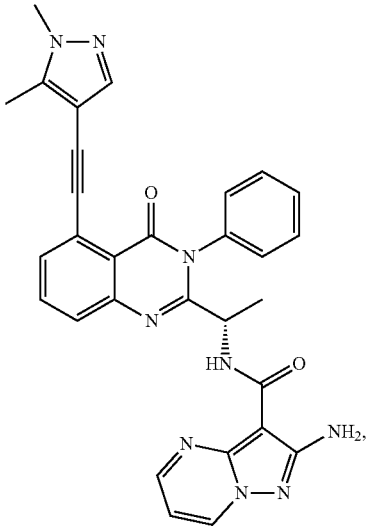
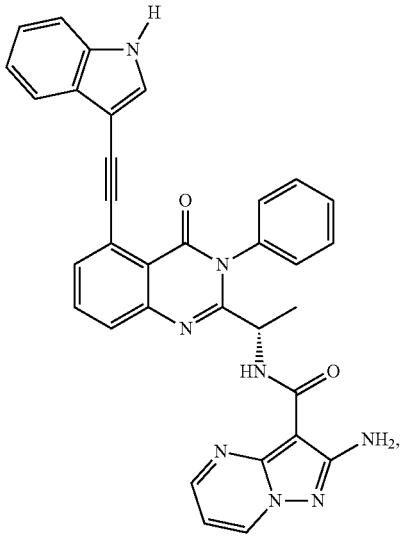
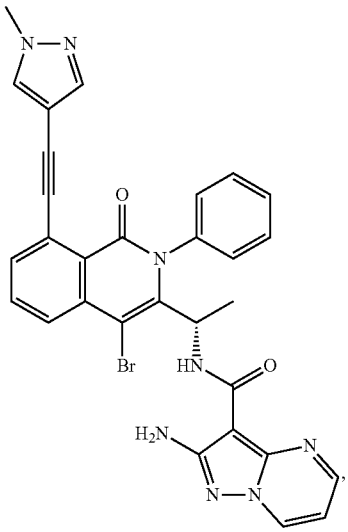
Compound 1013 	Compound 1016 
Compound 1014 	Compound 1017 
Compound 1015 	Compound 1018 

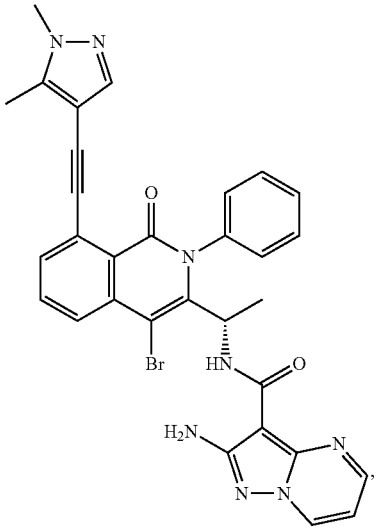
TABLE 4-continued

TABLE 4-continued

Compound 1041



Compound 1042



Compound 1043

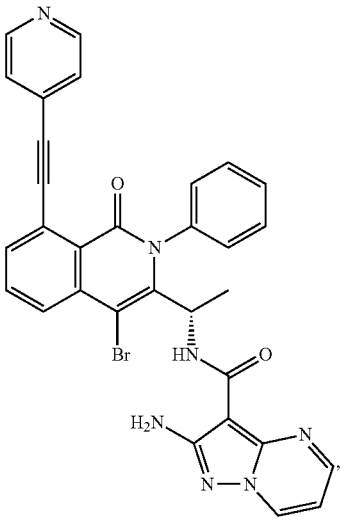
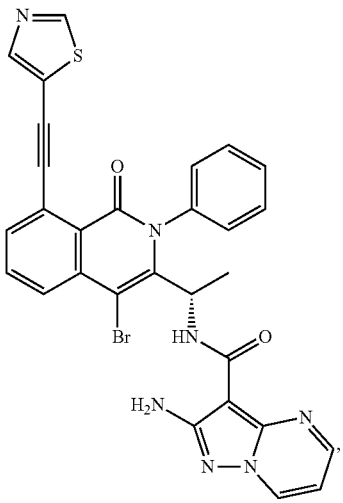
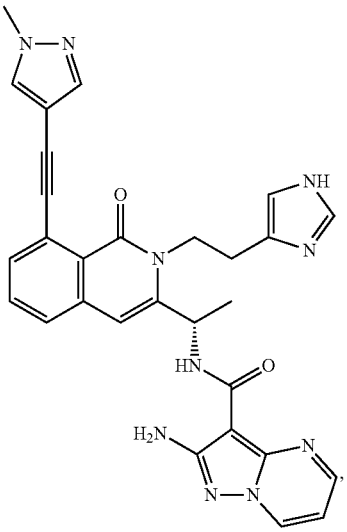


TABLE 4-continued

Compound 1044



Compound 1045



Compound 1046

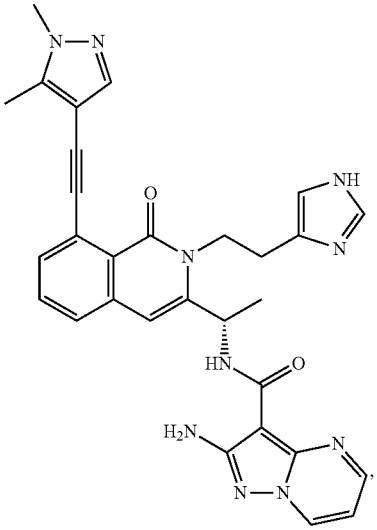
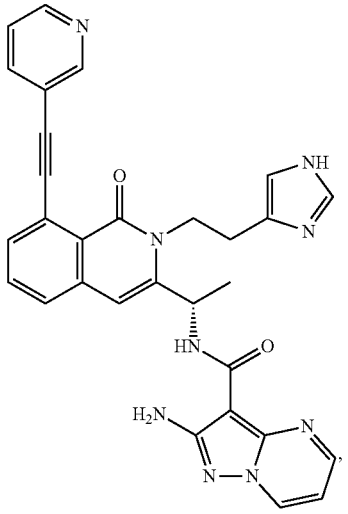
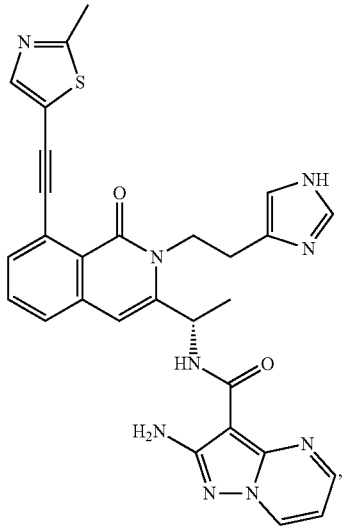


TABLE 4-continued

Compound 1047



Compound 1048



Compound 1049

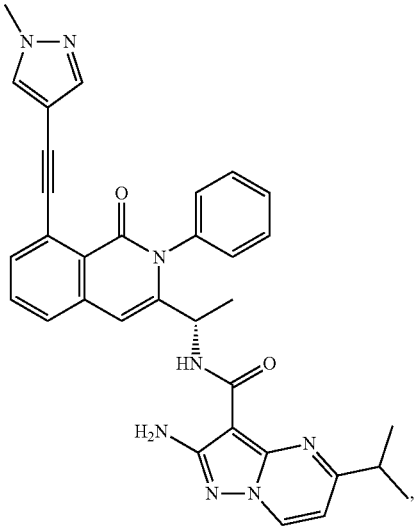
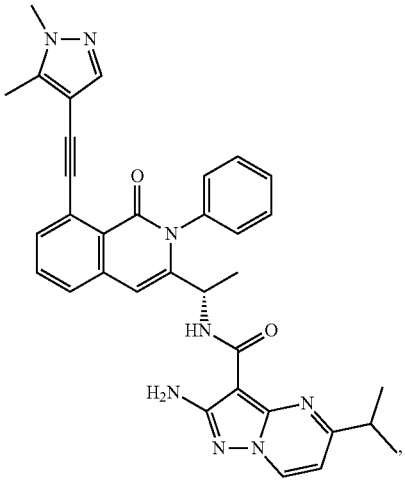
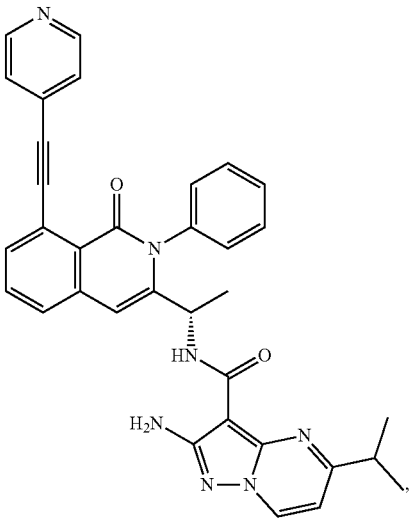


TABLE 4-continued

Compound 1050



Compound 1051



Compound 1052

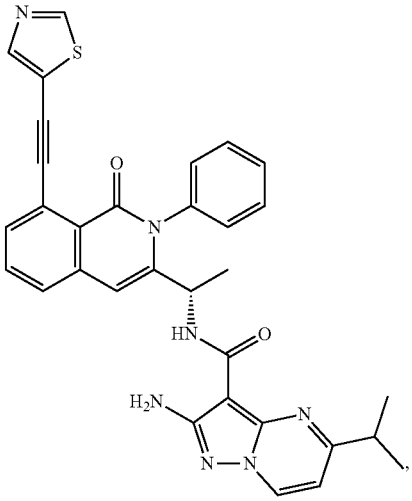
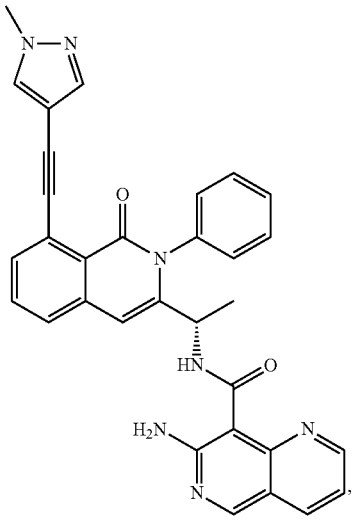
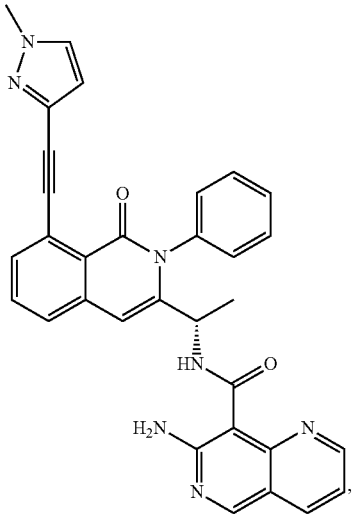


TABLE 4-continued

Compound 1053



Compound 1054



Compound 1055

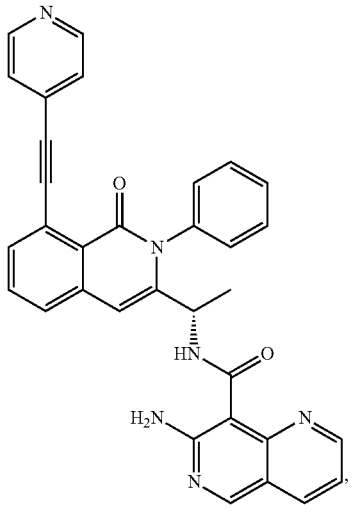
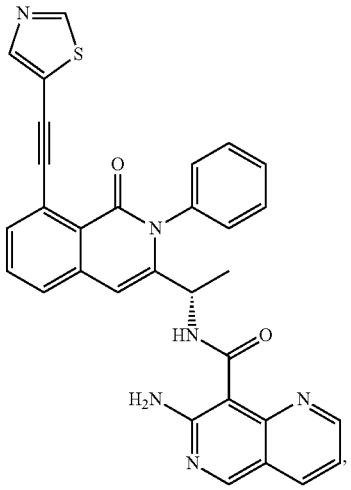
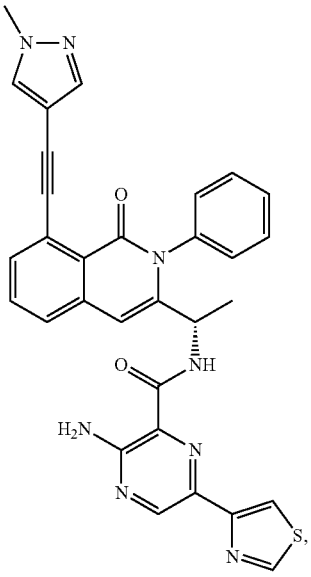


TABLE 4-continued

Compound 1056



Compound 1057



Compound 1058

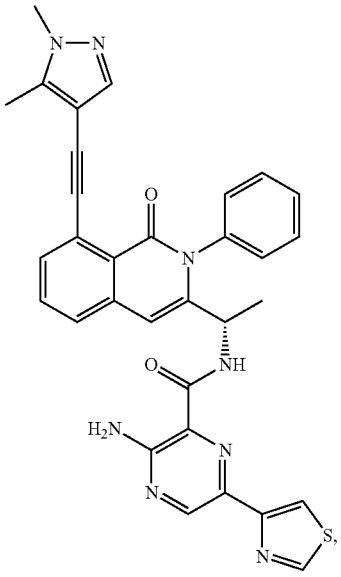
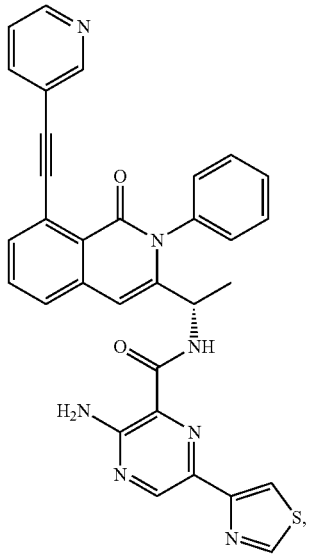


TABLE 4-continued

Compound 1059



Compound 1060

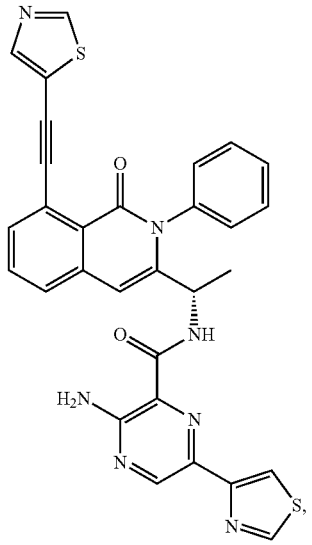
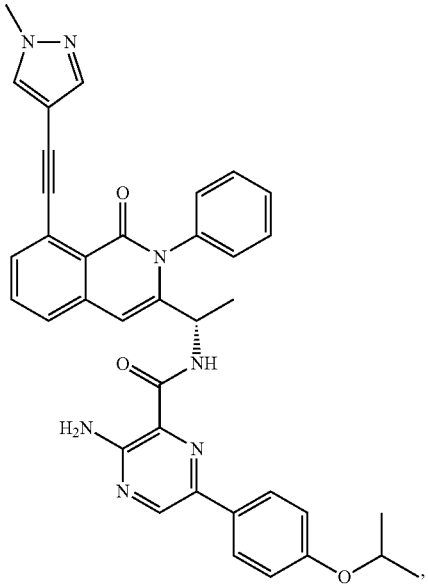


TABLE 4-continued

Compound 1061



Compound 1062

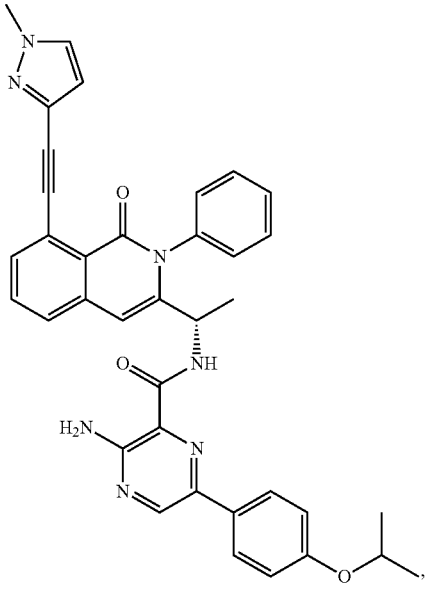


TABLE 4-continued

Compound 1063

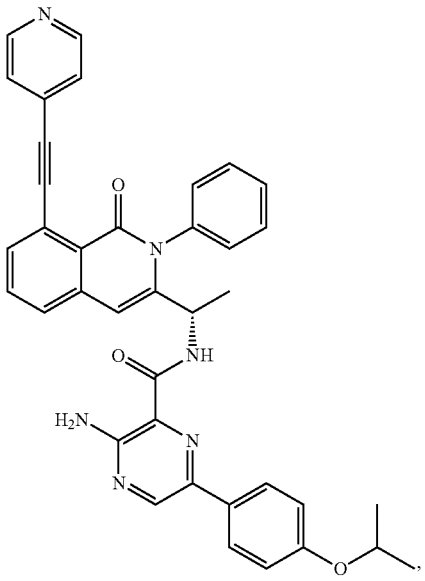
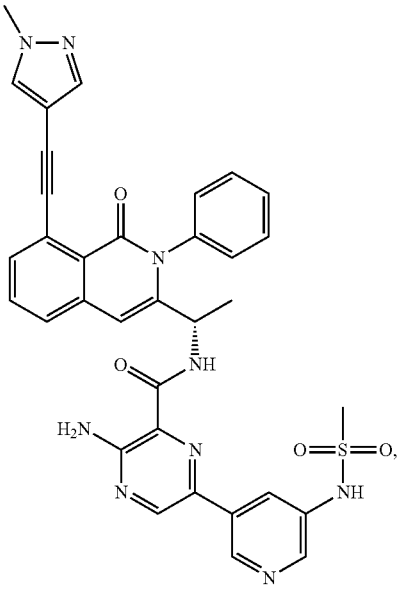
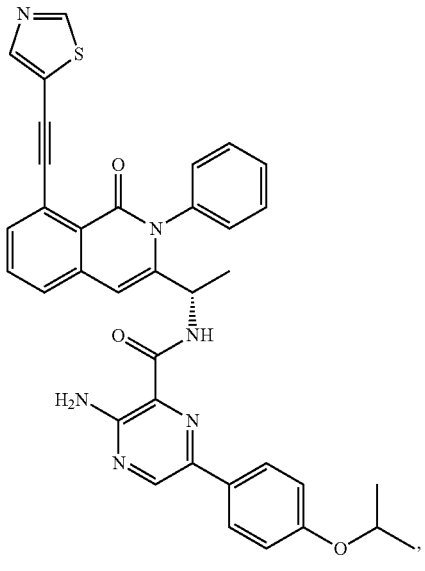


TABLE 4-continued

Compound 1065



Compound 1064



Compound 1066

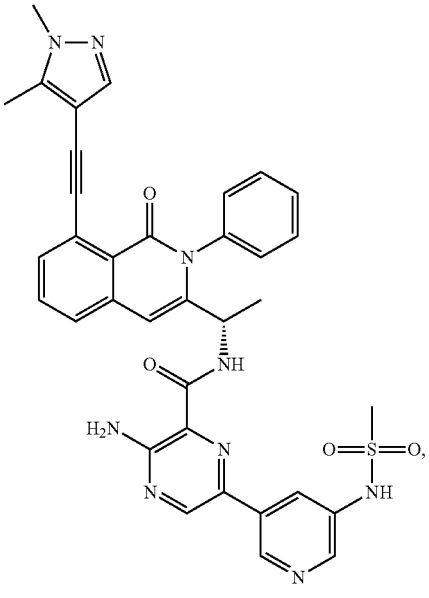
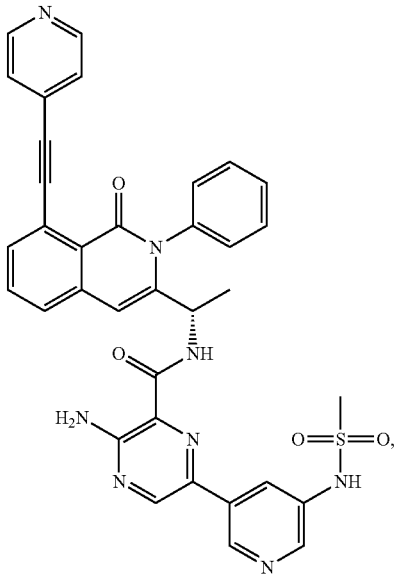


TABLE 4-continued

Compound 1067



Compound 1068

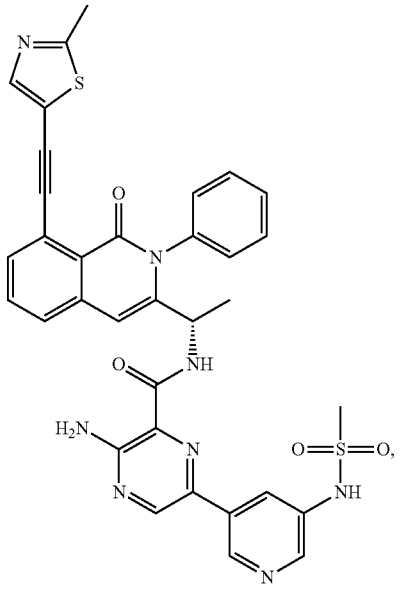
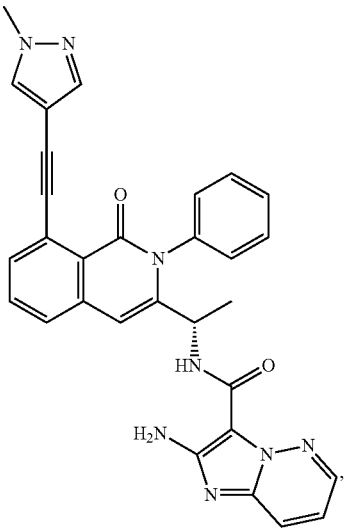
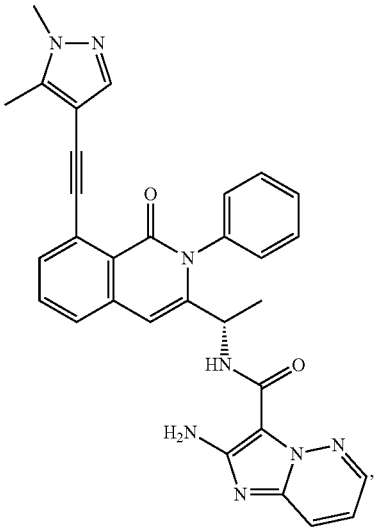


TABLE 4-continued

Compound 1069



Compound 1070



Compound 1071

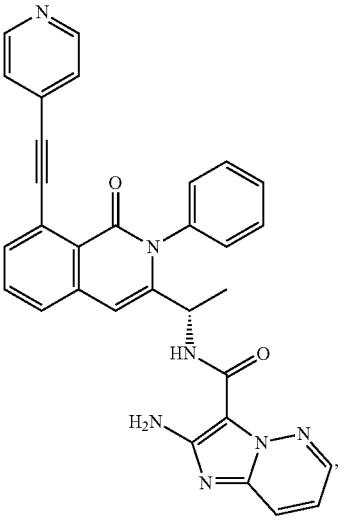
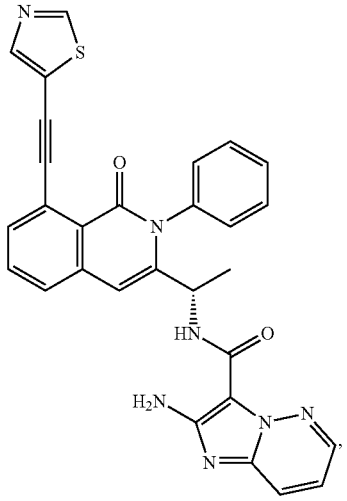
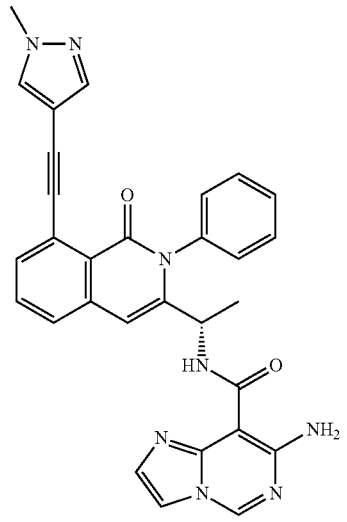


TABLE 4-continued

Compound 1072



Compound 1073



Compound 1074

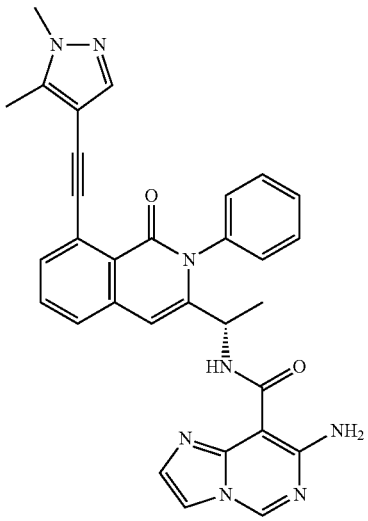
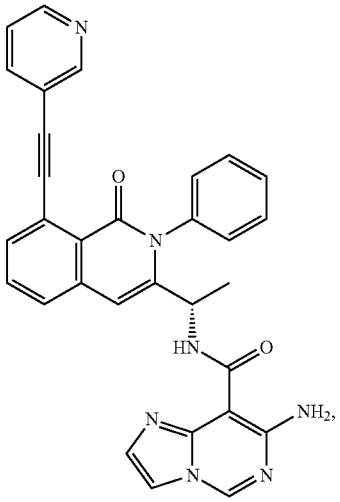
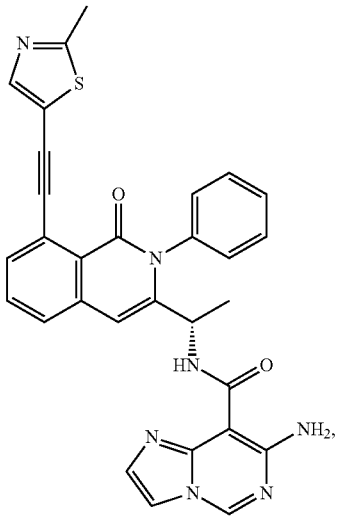


TABLE 4-continued

Compound 1075



Compound 1076



Compound 1077

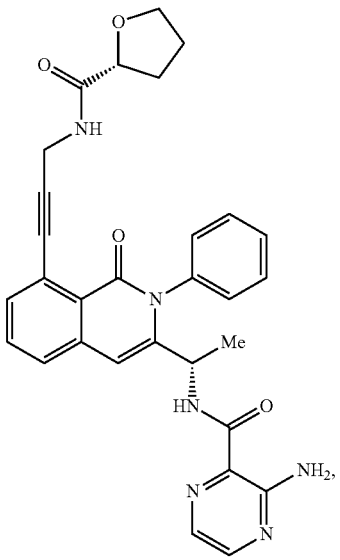


TABLE 4-continued

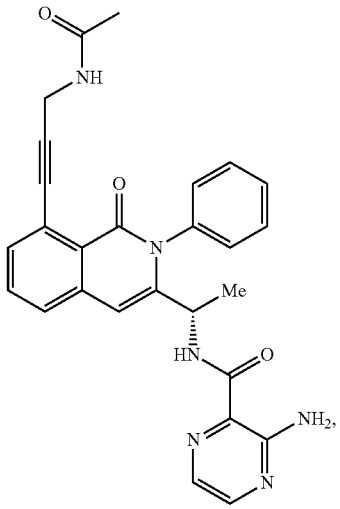
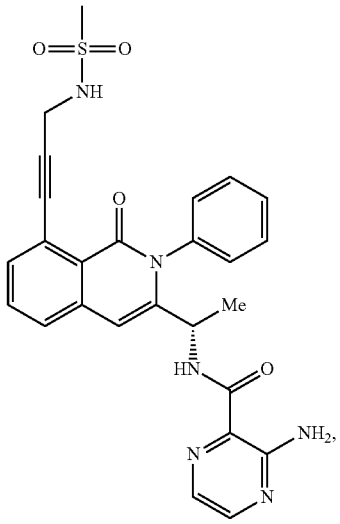
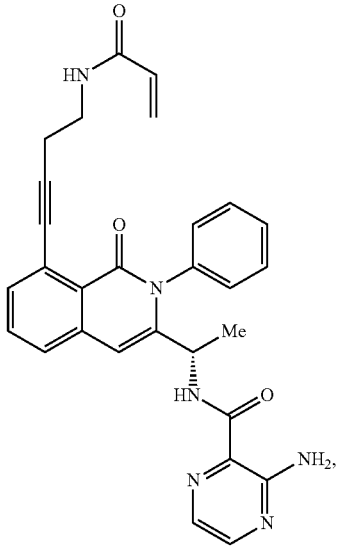
Compound 1078	
Compound 1079	
Compound 1080	

TABLE 4-continued

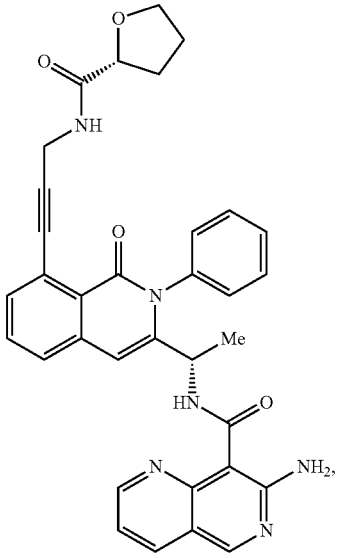
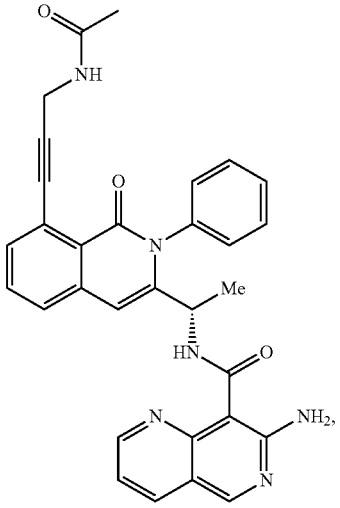
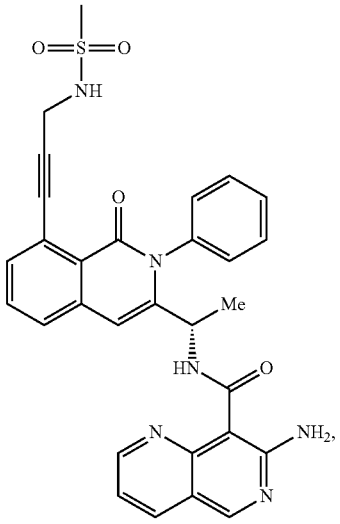
Compound 1081	
Compound 1082	
Compound 1083	

TABLE 4-continued

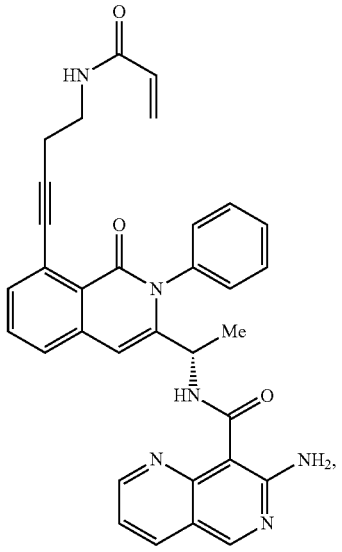
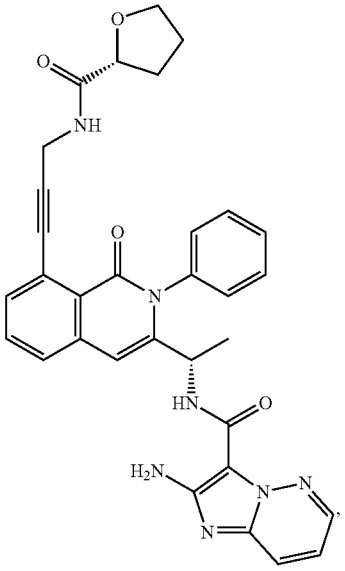
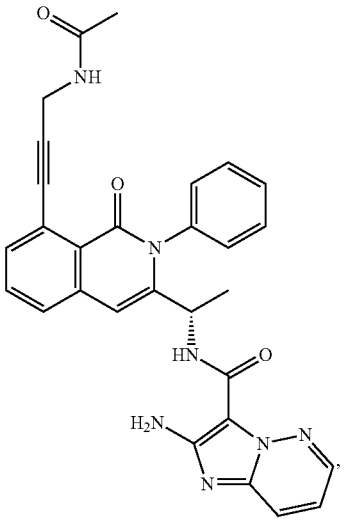
Compound 1084	
Compound 1085	
Compound 1086	

TABLE 4-continued

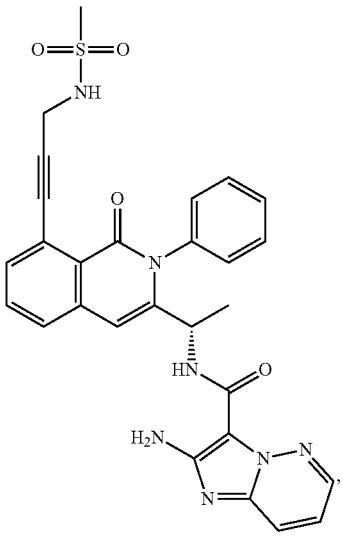
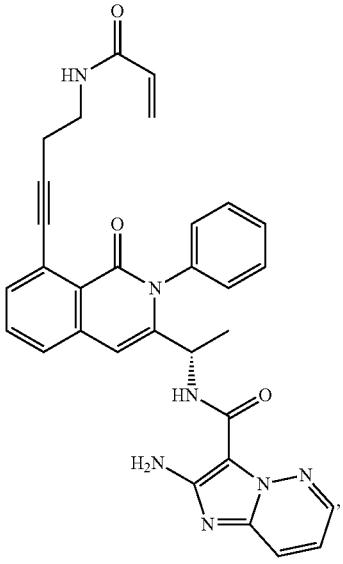
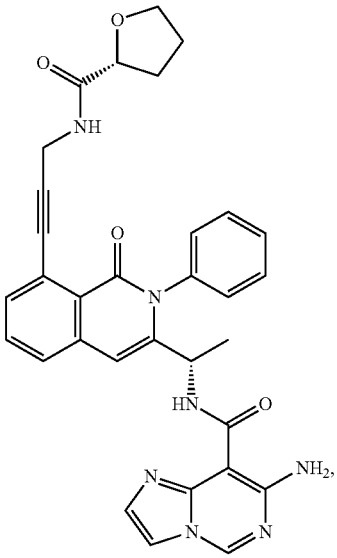
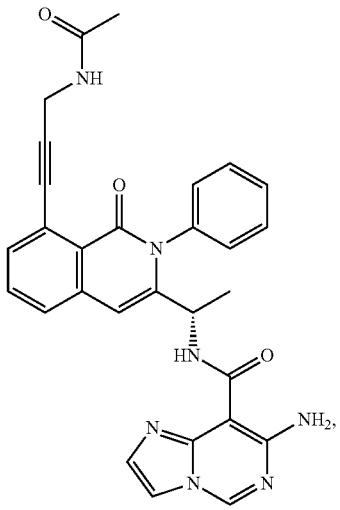
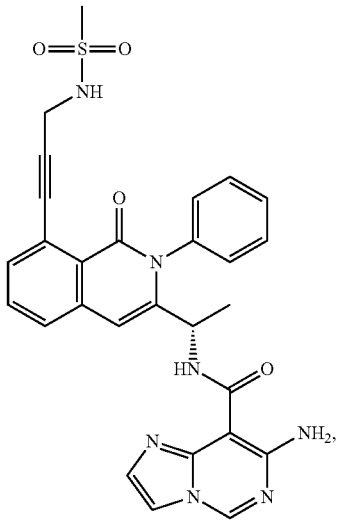
Compound 1087	
Compound 1088	
Compound 1089	

TABLE 4-continued

Compound 1090



Compound 1091



Compound 1092

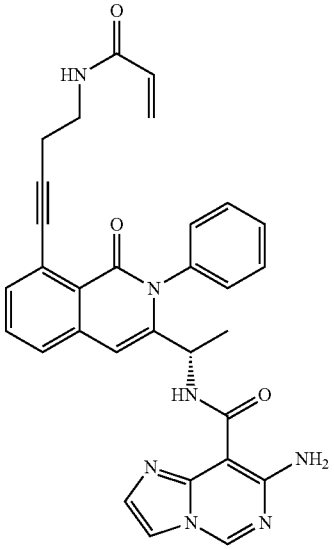
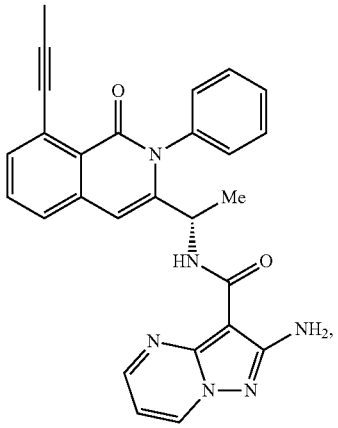
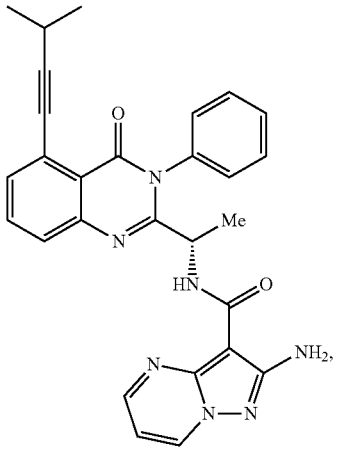


TABLE 5

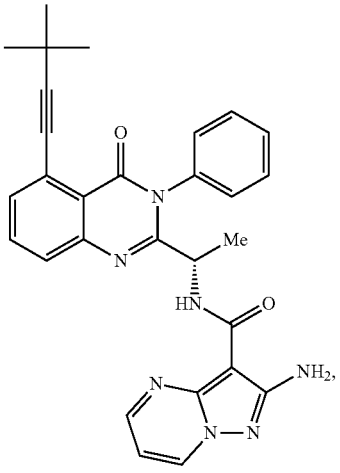
Compound 2001



Compound 2002



Compound 2003



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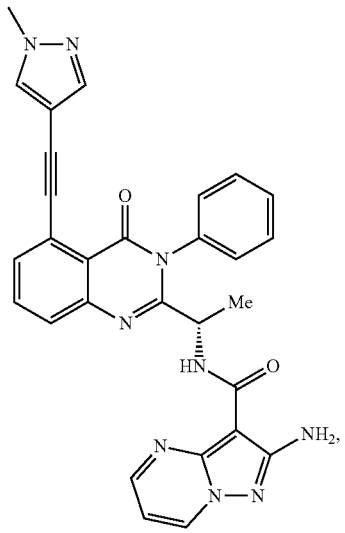

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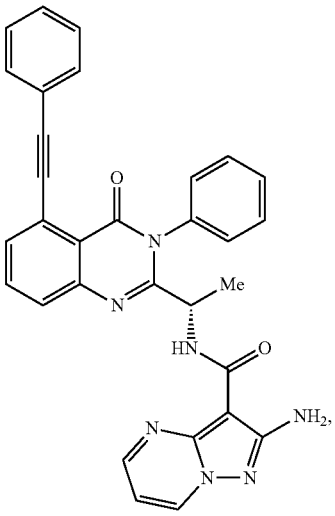

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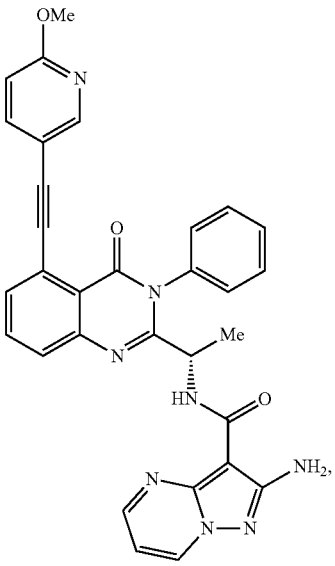

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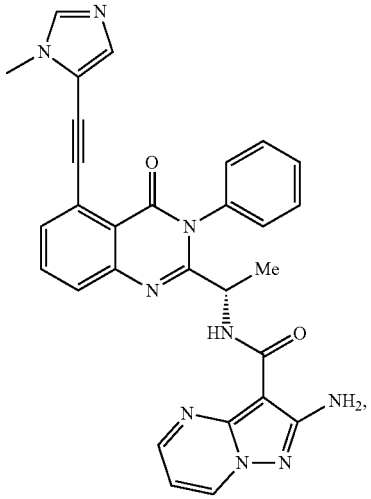

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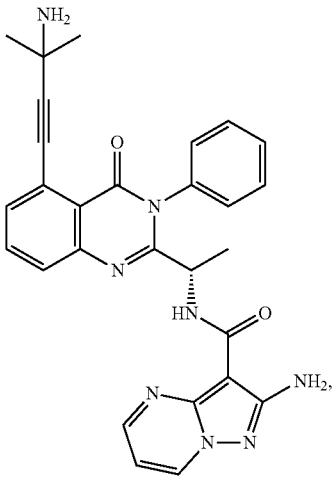

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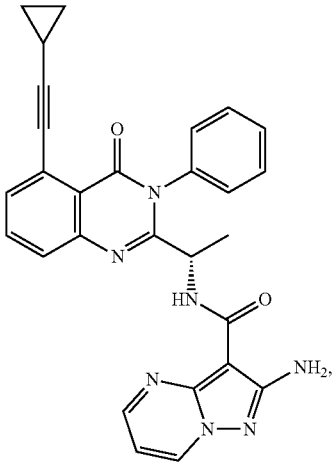

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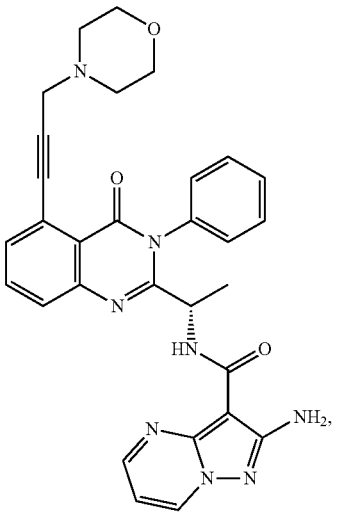
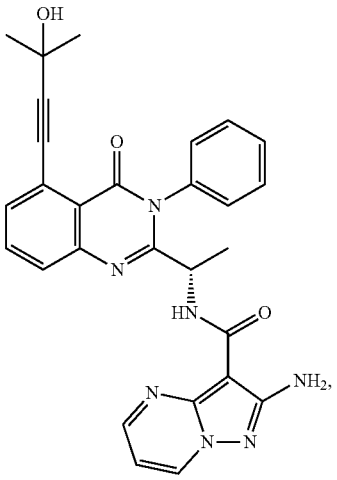
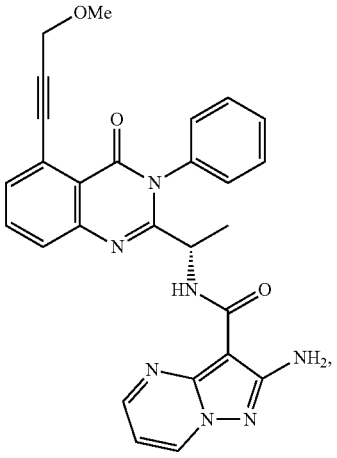
Compound 2010	
Compound 2011	
Compound 2012	

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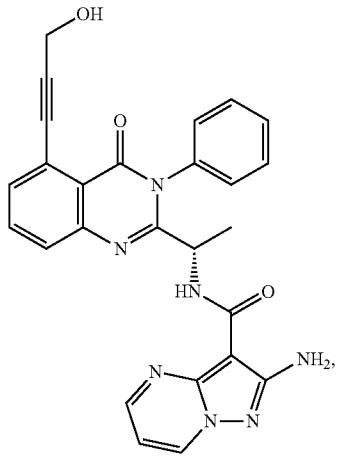
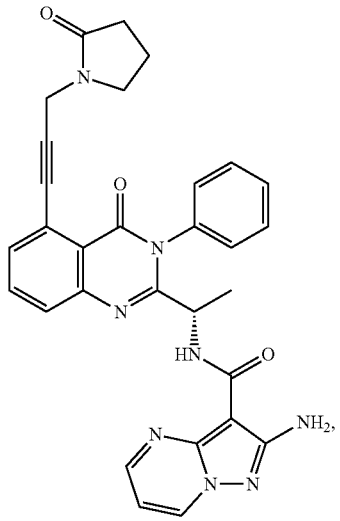
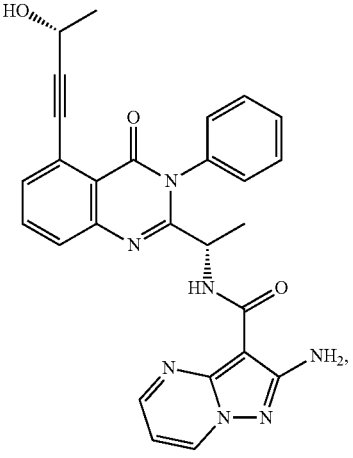
Compound 2013	
Compound 2014	
Compound 2015	

TABLE 5-continued

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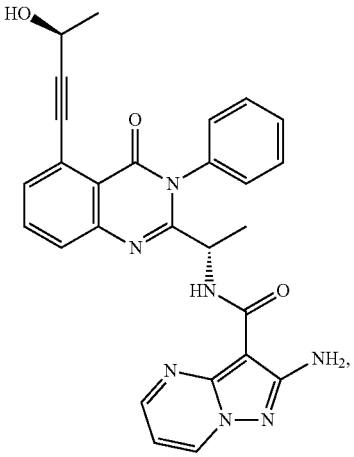

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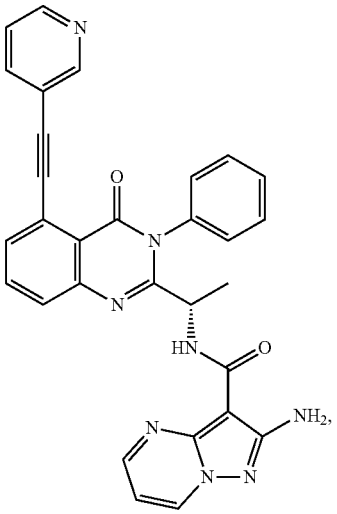

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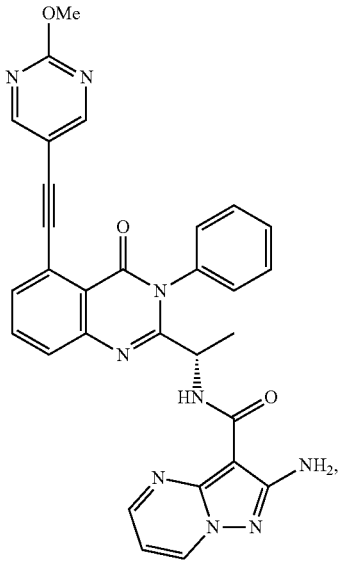

TABLE 5-continued

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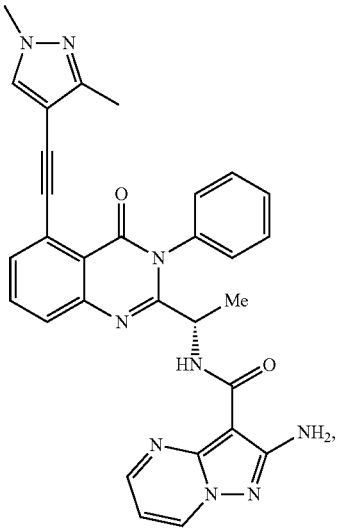

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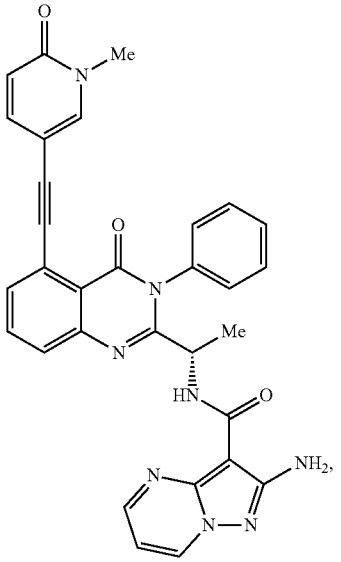

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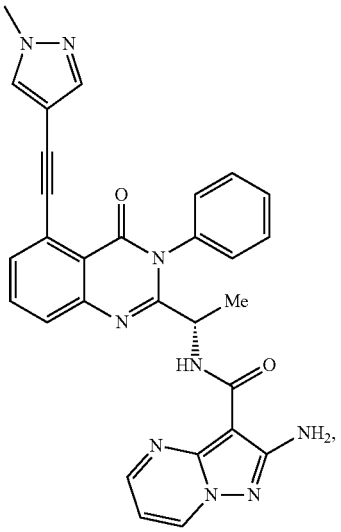

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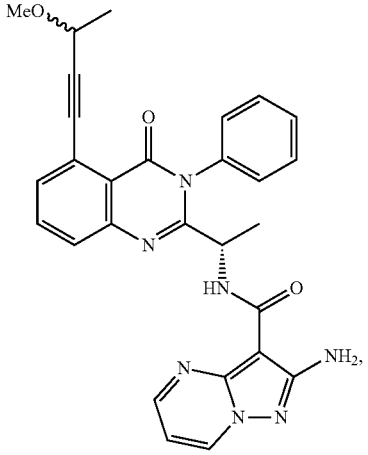
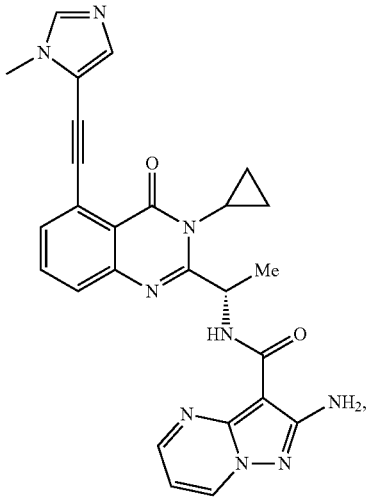
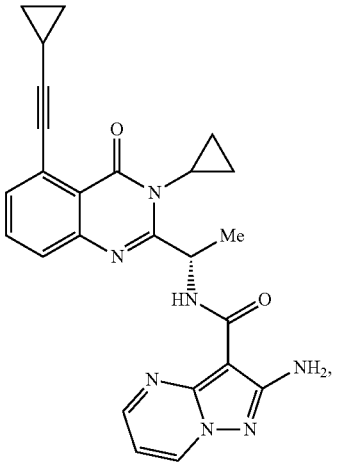
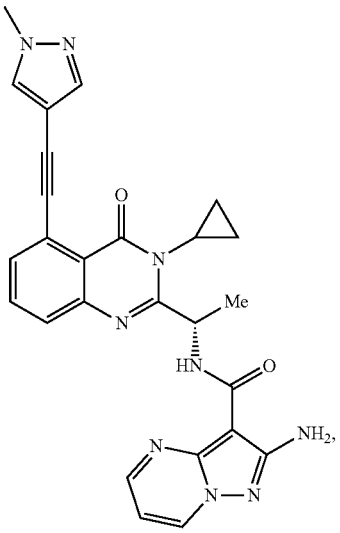
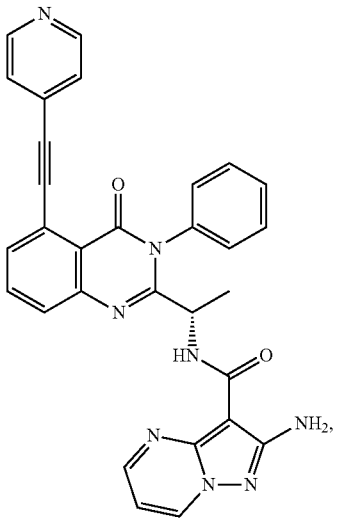
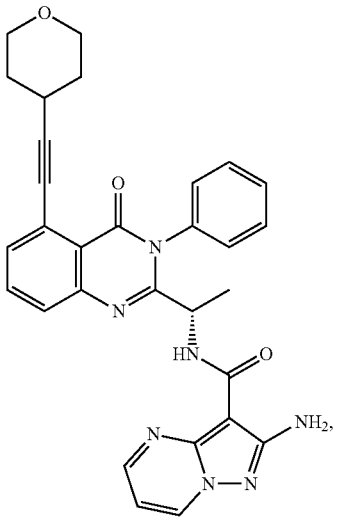
Compound 2022	
Compound 2023	
Compound 2024	

TABLE 5-continued

Compound 2025	
Compound 2026	
Compound 2027	

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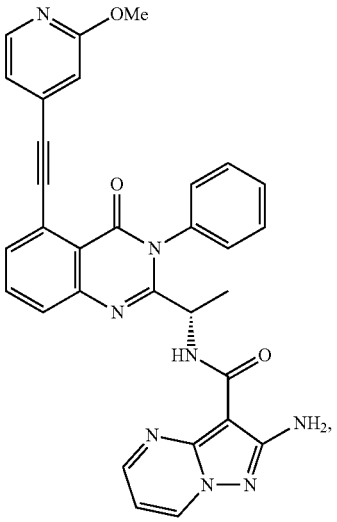
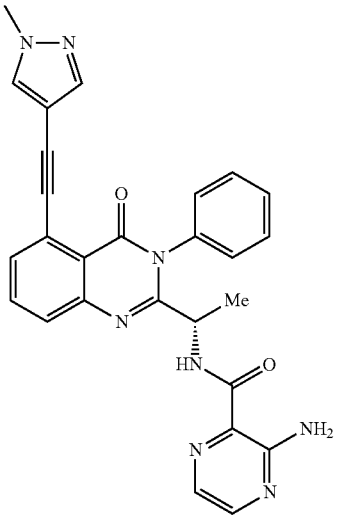
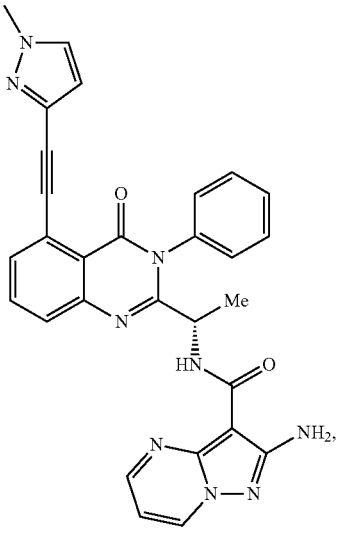
Compound 2028	
Compound 2029	
Compound 2030	

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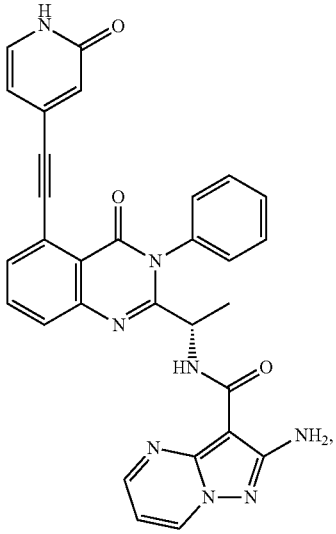
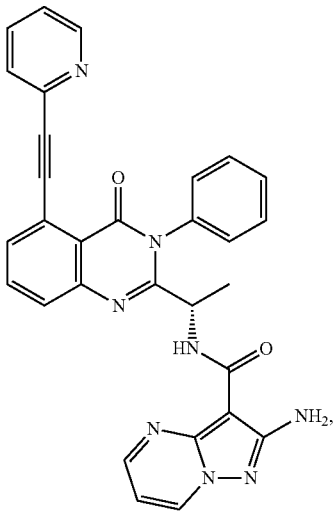
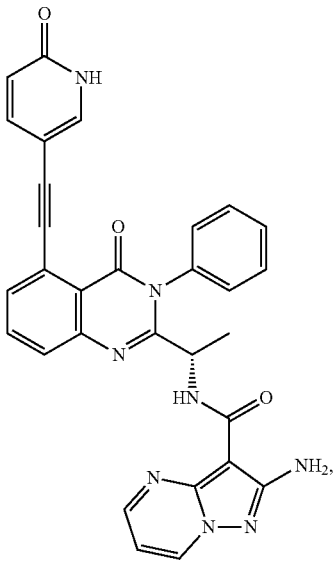
Compound 2031	
Compound 2032	
Compound 2033	

TABLE 5-continued

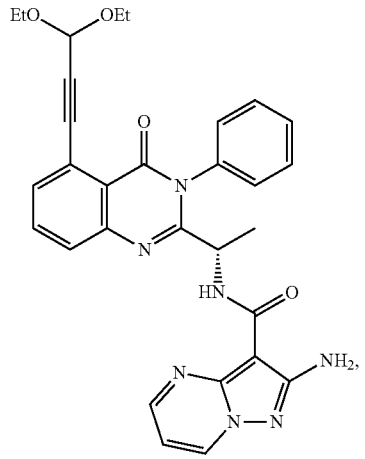
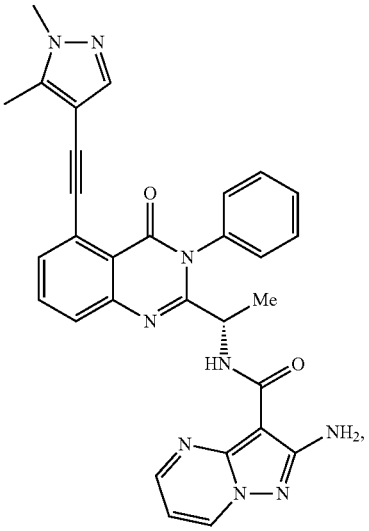
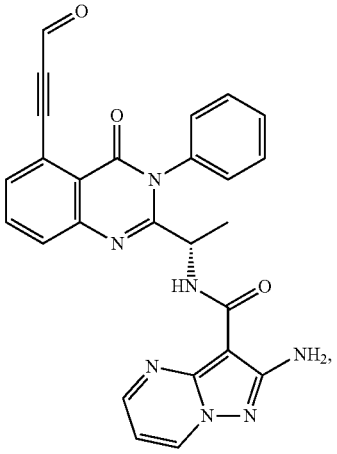
Compound 2034	
Compound 2035	
Compound 2036	

TABLE 5-continued

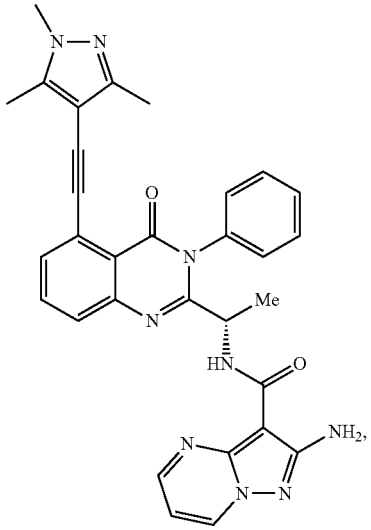
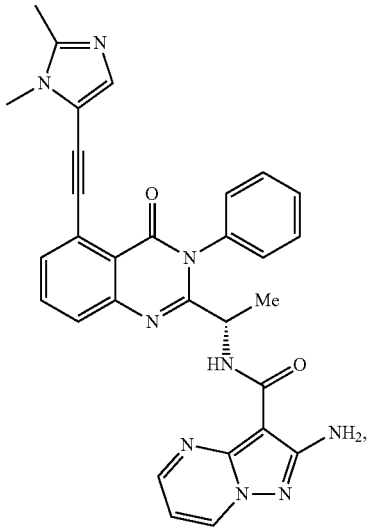
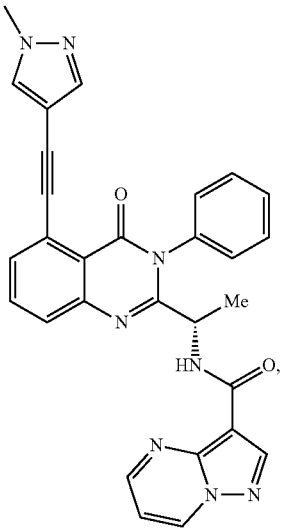
Compound 2037	
Compound 2038	
Compound 2039	

TABLE 5-continued

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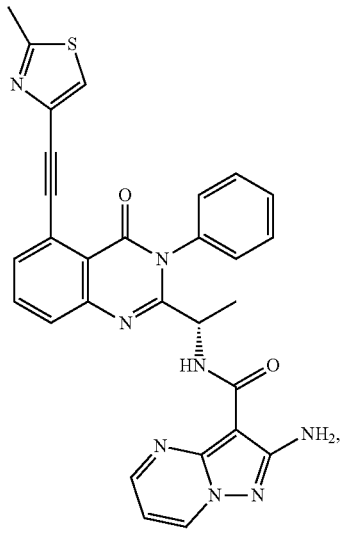
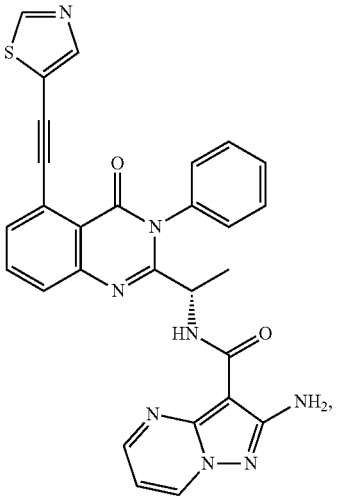


Compound 2041



Compound 2042

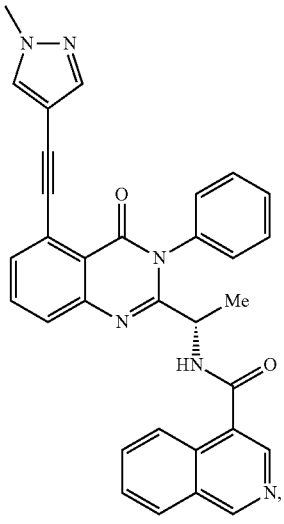


TABLE 5-continued

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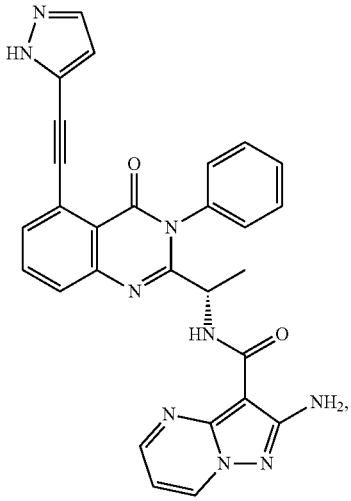
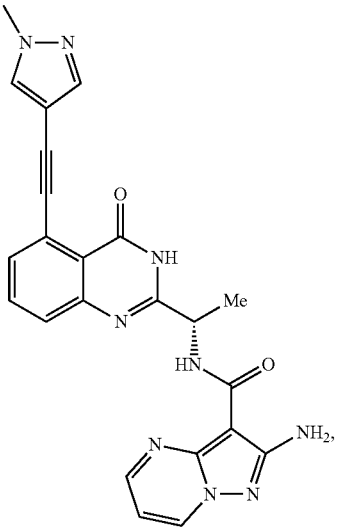


Compound 2044



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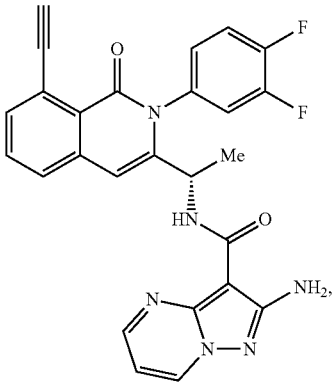


TABLE 5-continued

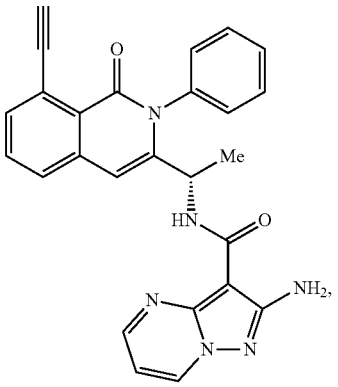
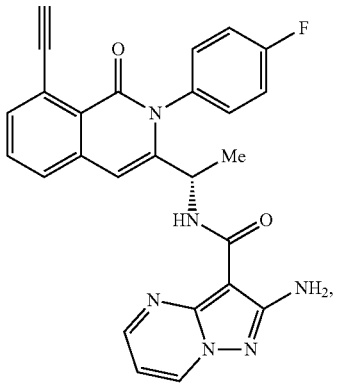
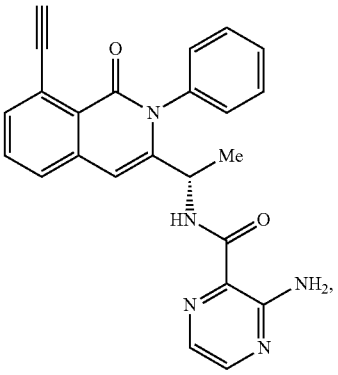
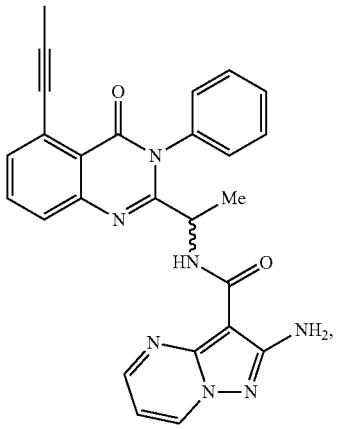
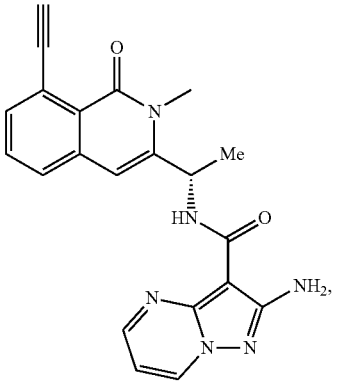
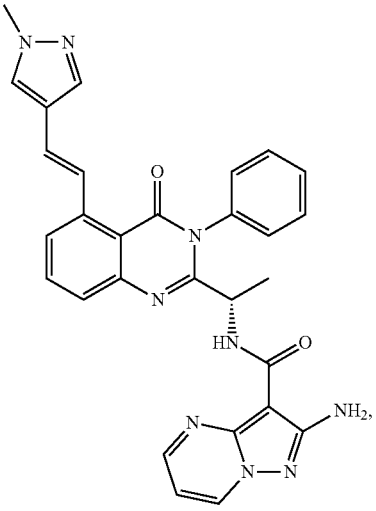
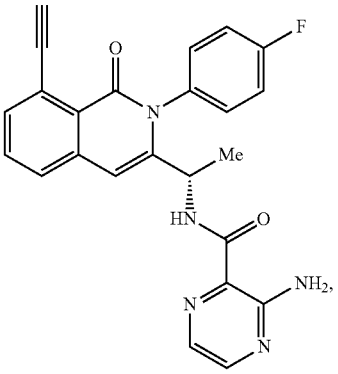
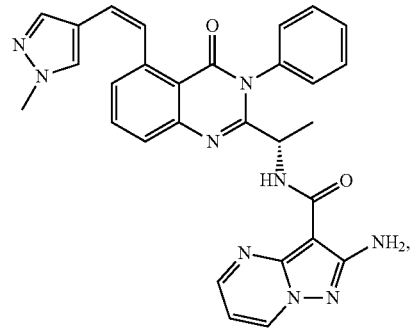
Compound 2046 	Compound 2050 
Compound 2047 	Compound 2051 
Compound 2048 	Compound 2052 
Compound 2049 	

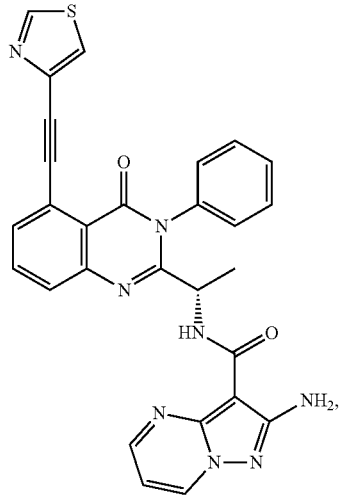
TABLE 5-continued

TABLE 5-continued

Compound 2053



Compound 2054



Compound 2055

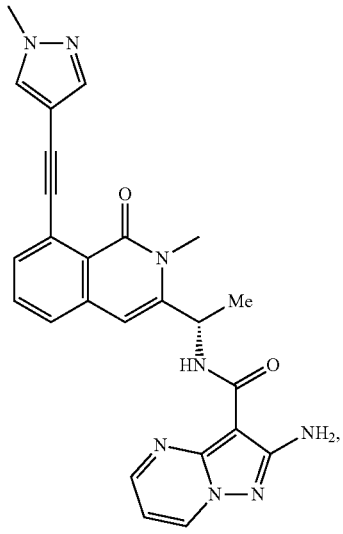
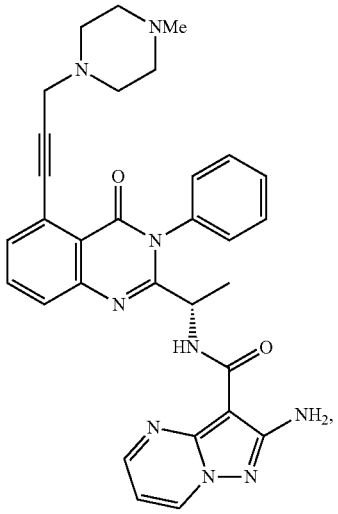
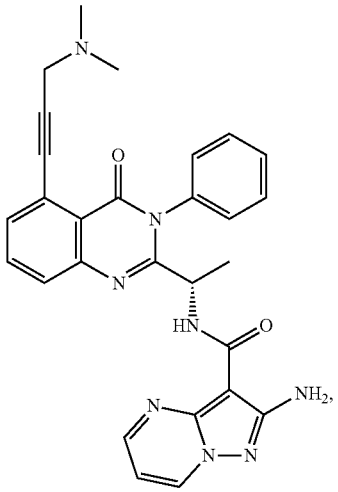


TABLE 5-continued

Compound 2056



Compound 2057



Compound 2058

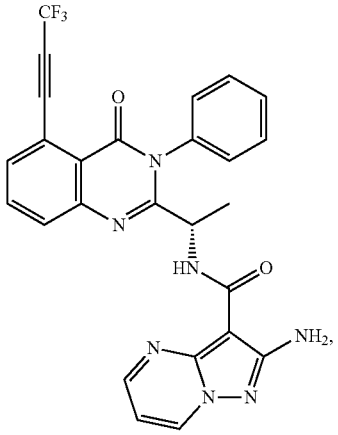
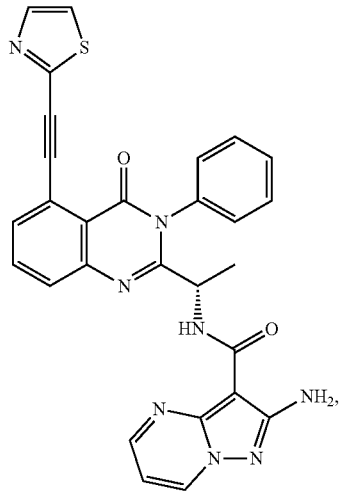
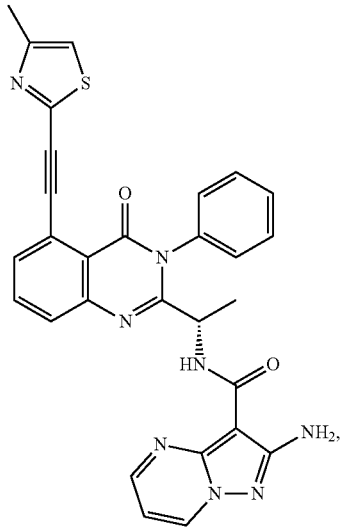


TABLE 5-continued

Compound 2059



Compound 2060



Compound 2061

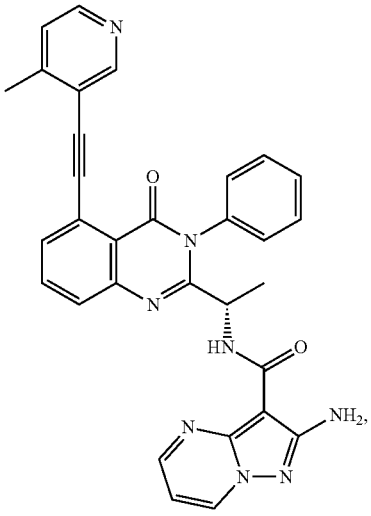
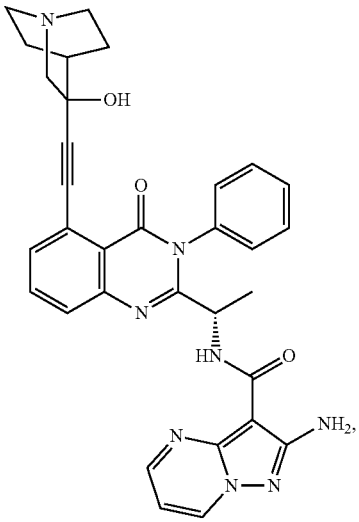
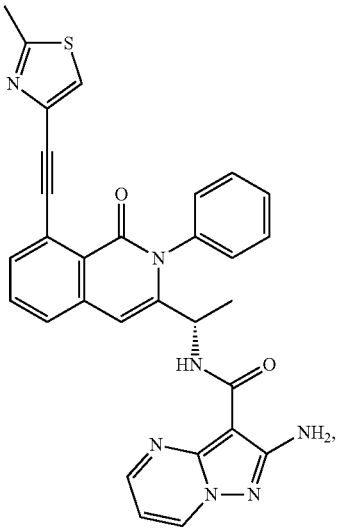


TABLE 5-continued

Compound 2062



Compound 2063



Compound 2064

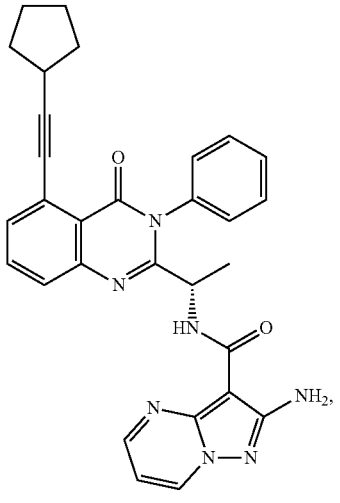
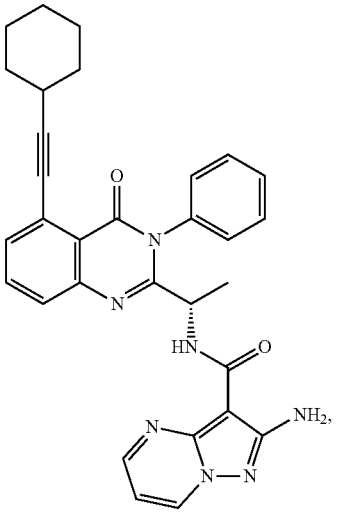
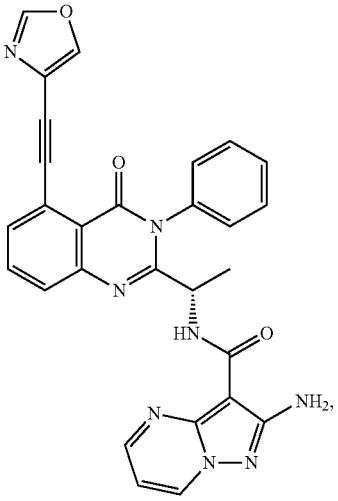


TABLE 5-continued

Compound 2065



Compound 2066



Compound 2067

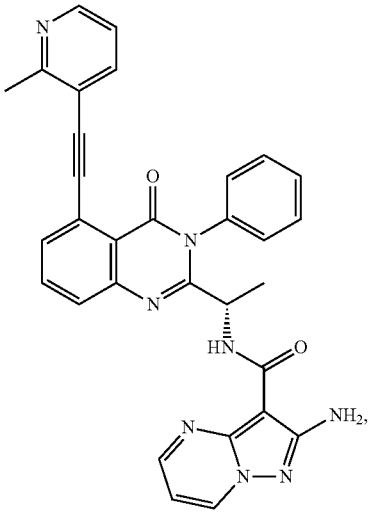
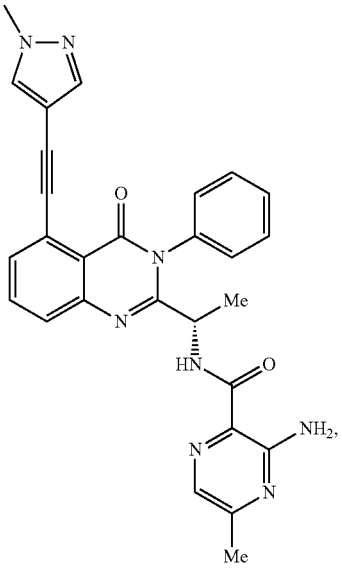
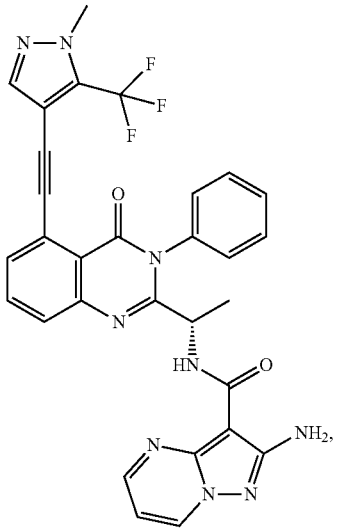


TABLE 5-continued

Compound 2068



Compound 2069



Compound 2070

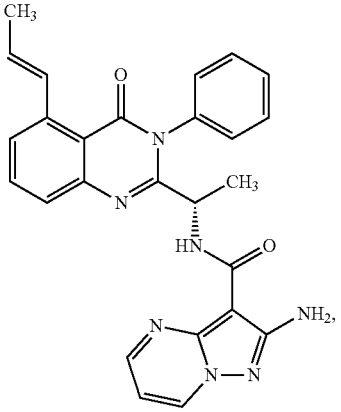


TABLE 5-continued

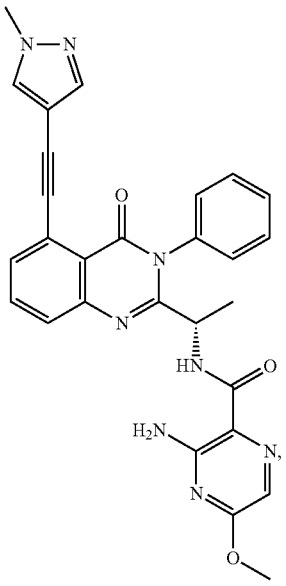
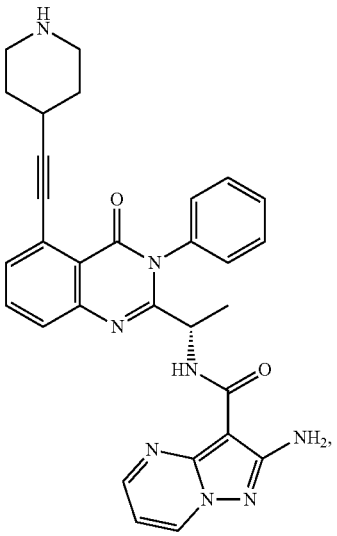
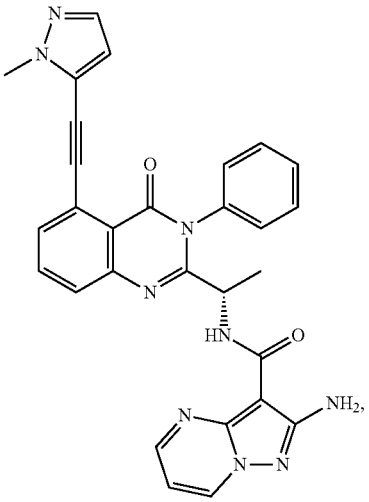
Compound 2071	
Compound 2072	
Compound 2073	

TABLE 5-continued

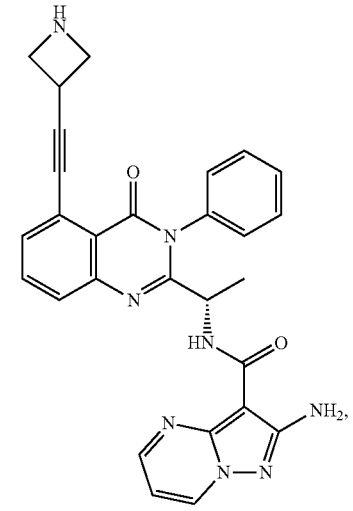
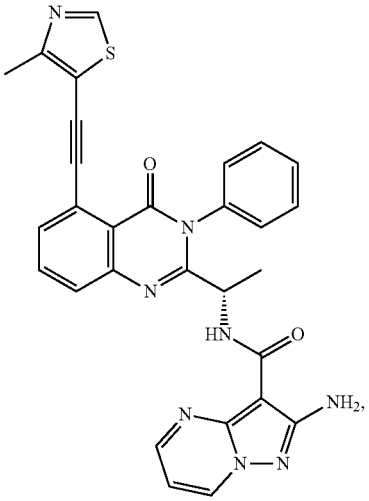
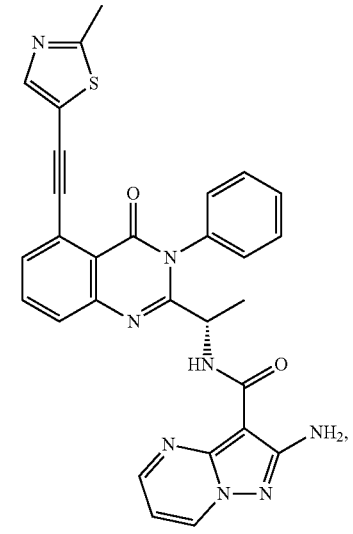
Compound 2074	
Compound 2075	
Compound 2076	

TABLE 5-continued

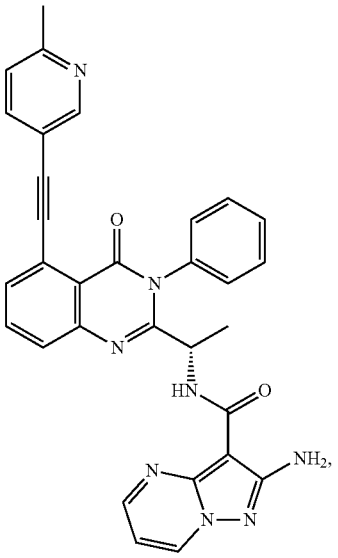
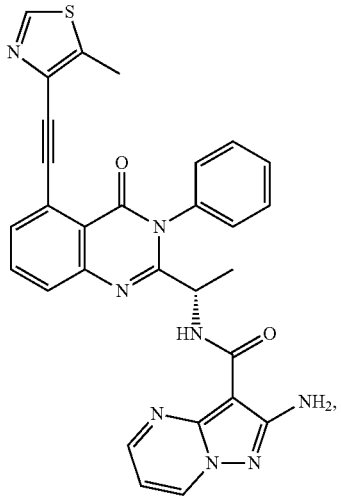
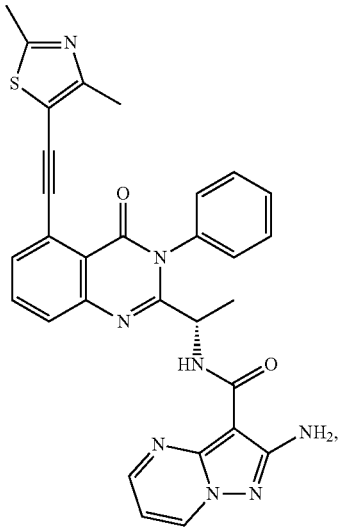
Compound 2077	
Compound 2078	
Compound 2079	

TABLE 5-continued

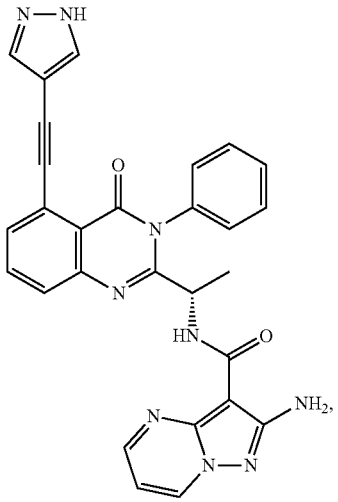
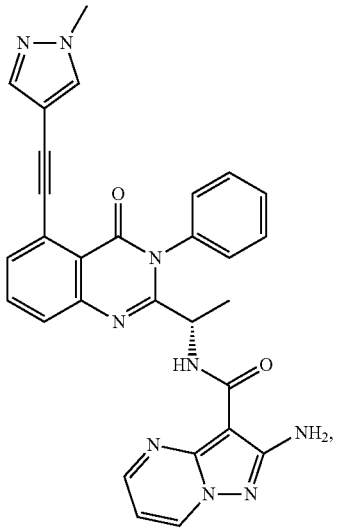
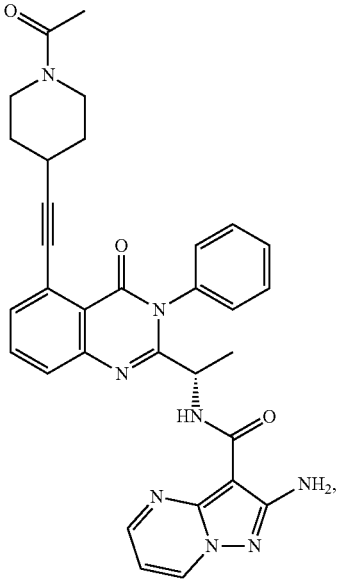
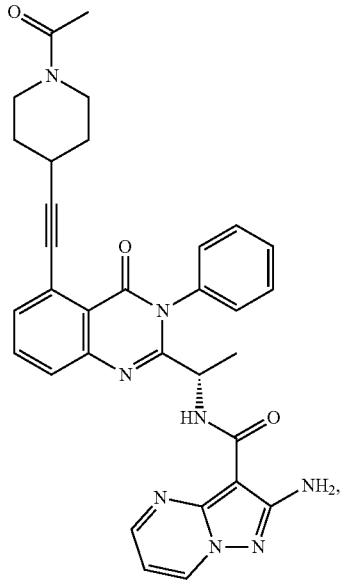
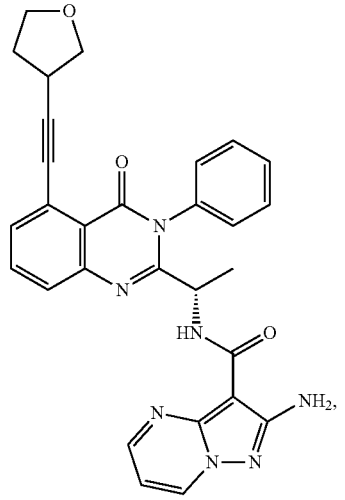
Compound 2080	
Compound 2081	
Compound 2082	

TABLE 5-continued

Compound 2083



Compound 2084



Compound 2085

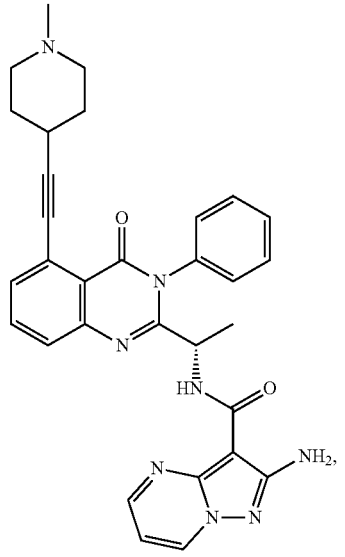
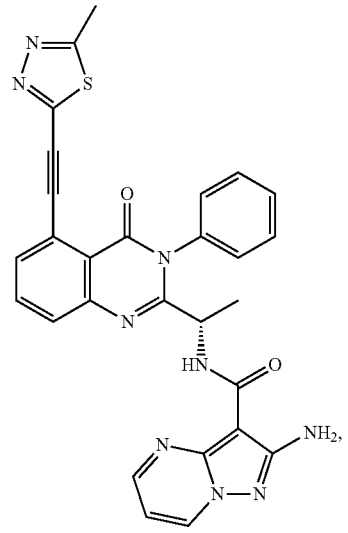
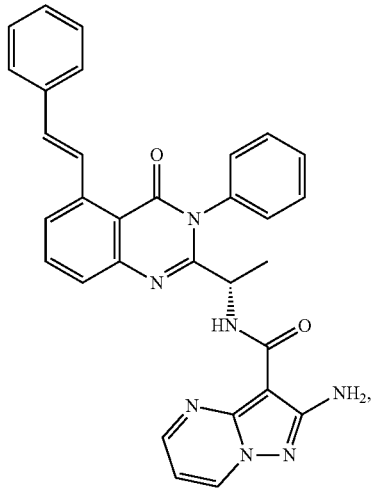


TABLE 5-continued

Compound 2086



Compound 2087



Compound 2088

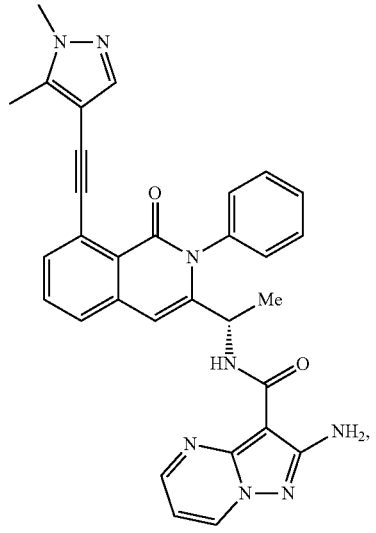


TABLE 5-continued

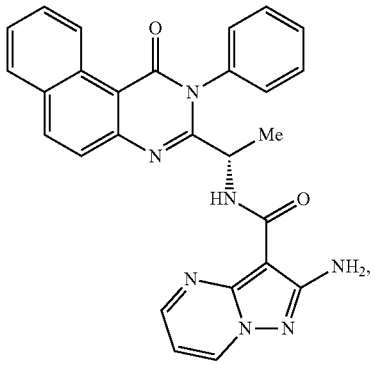
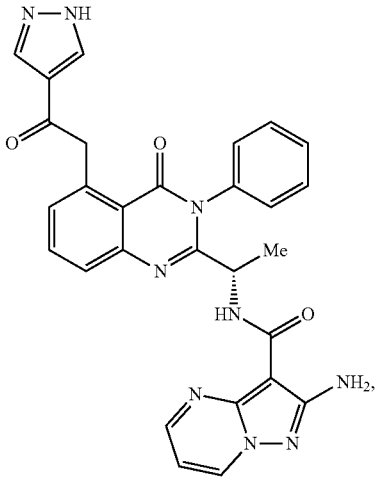
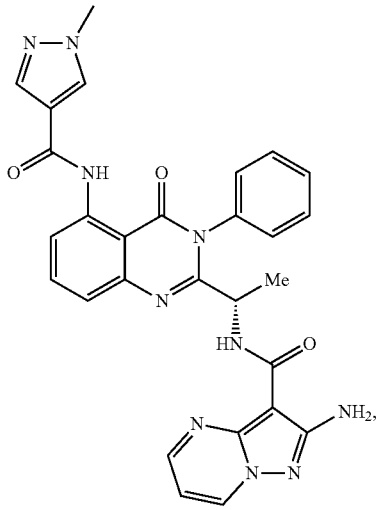
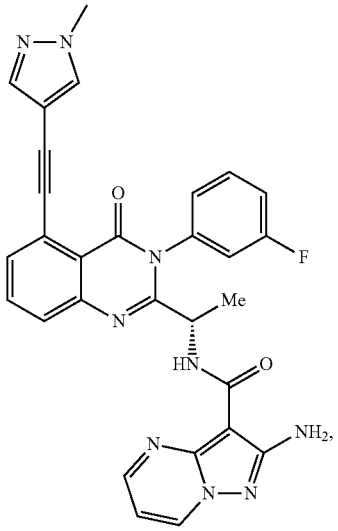
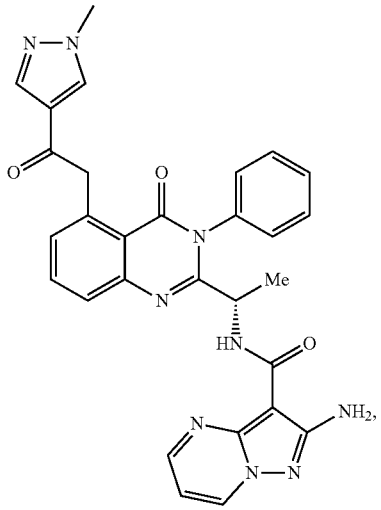
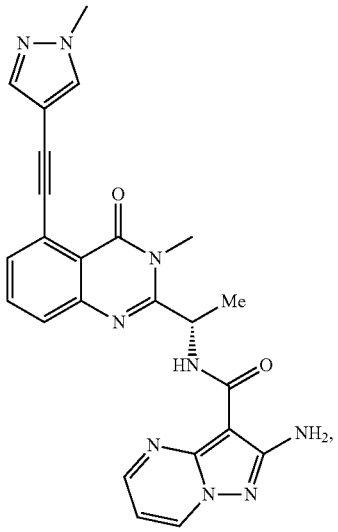
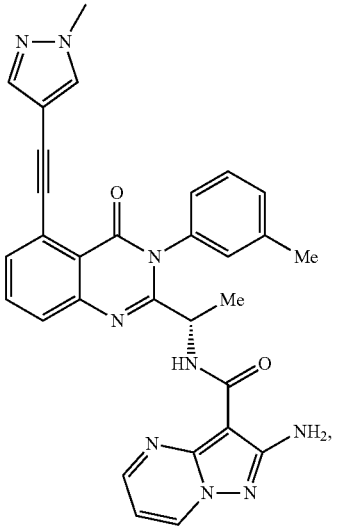
Compound 2089 	Compound 2092 
Compound 2090 	Compound 2093 
Compound 2091 	Compound 2094 

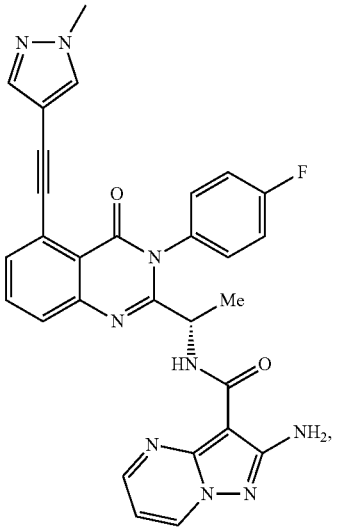
TABLE 5-continued

TABLE 5-continued

Compound 2095



Compound 2096



Compound 2097

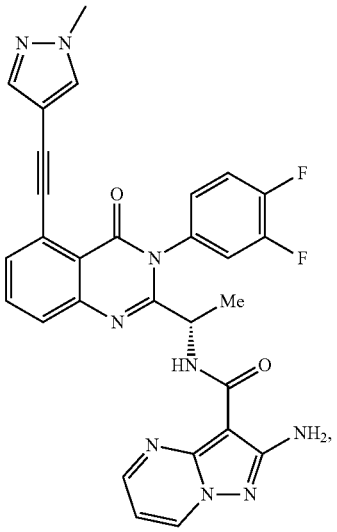
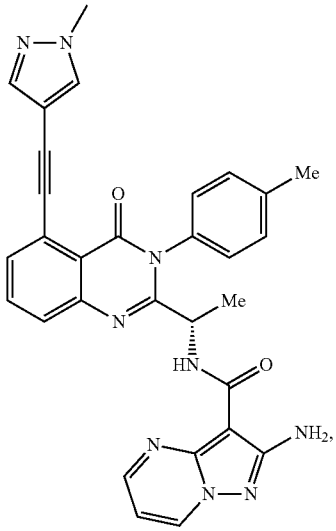
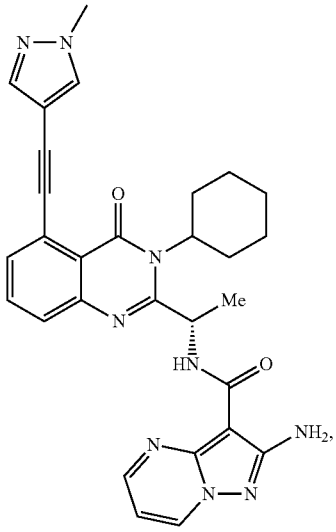


TABLE 5-continued

Compound 2098



Compound 2099



Compound 2100

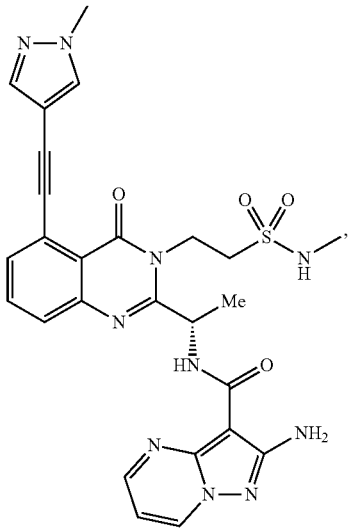
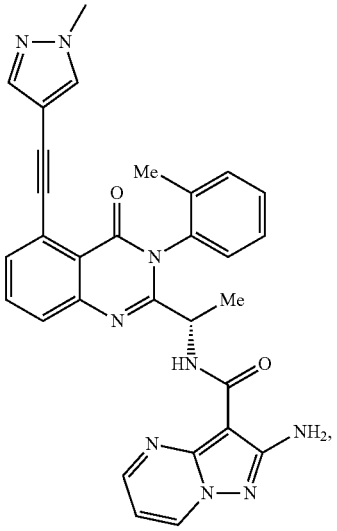
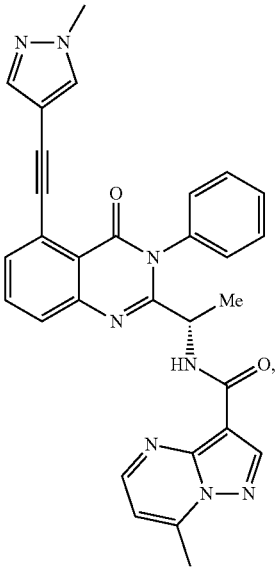


TABLE 5-continued

Compound 2101



Compound 2102



Compound 2103

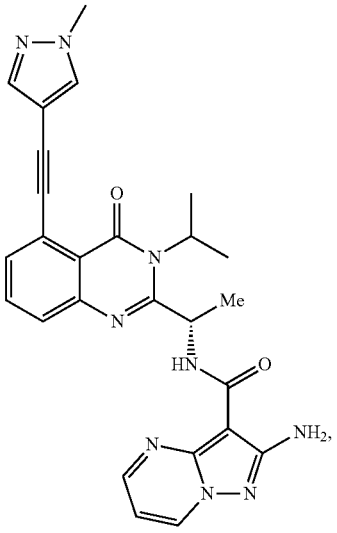
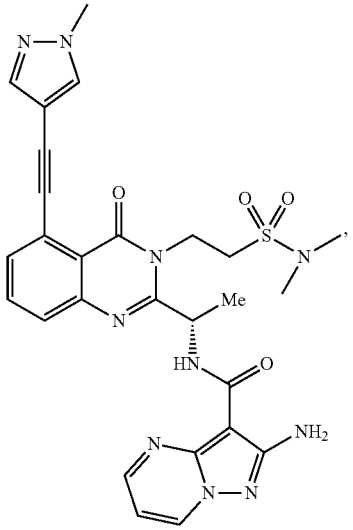
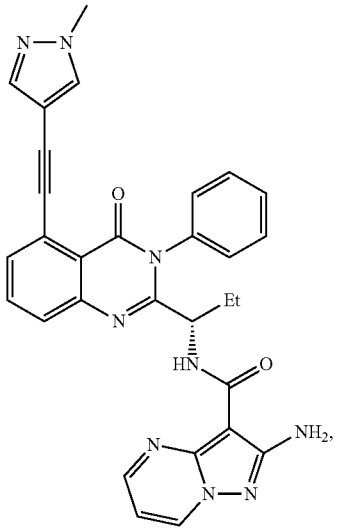


TABLE 5-continued

Compound 2104



Compound 2105



Compound 2106

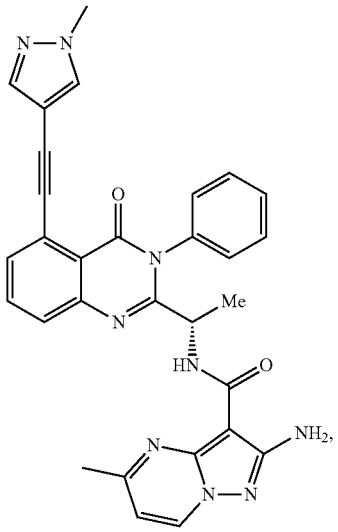
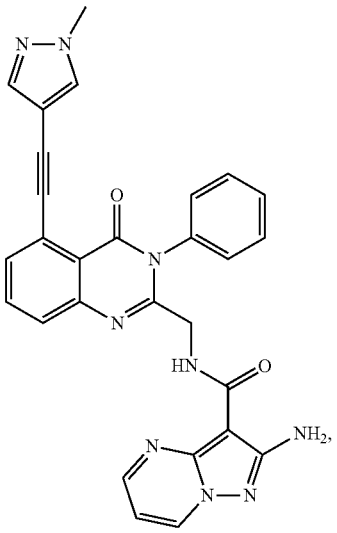
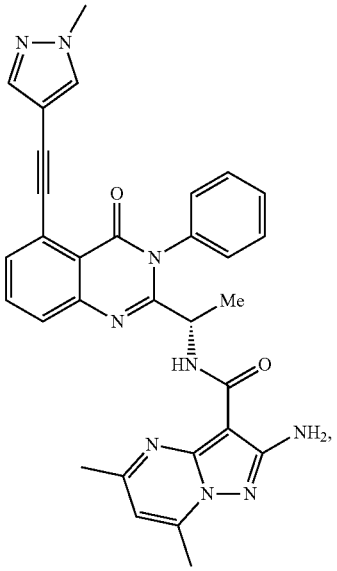


TABLE 5-continued

Compound 2107



Compound 2108



Compound 2109

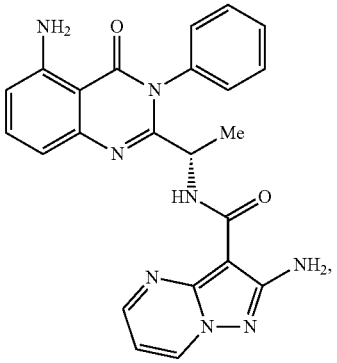
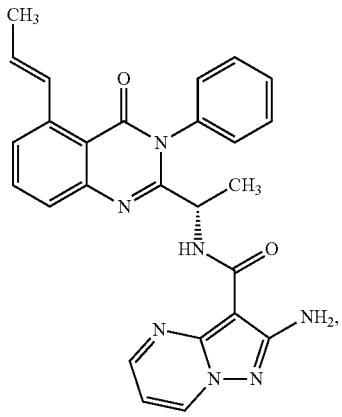
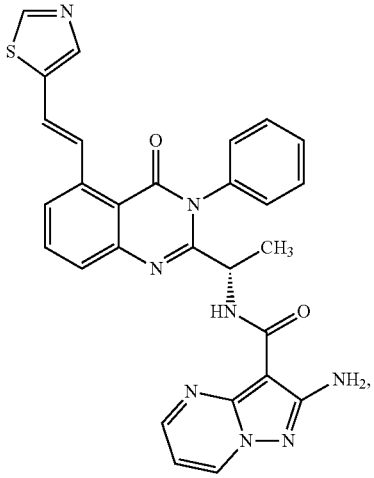


TABLE 6

Compound 3001BB



Compound 3002



Compound 3003

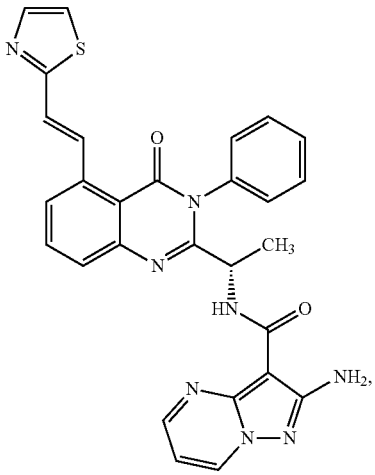
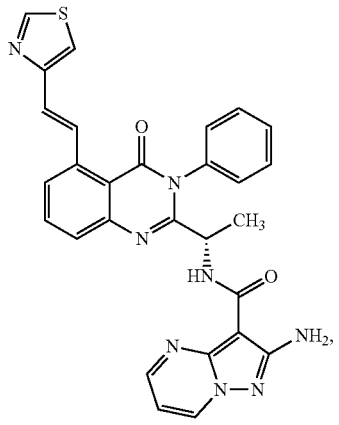
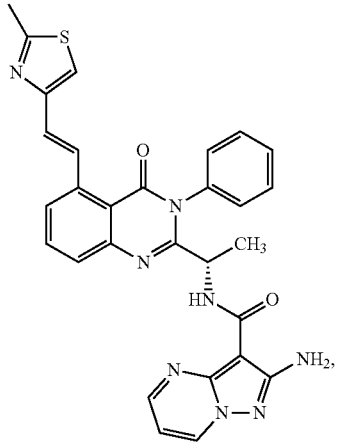


TABLE 6-continued

Compound 3004



Compound 3005



Compound 3006

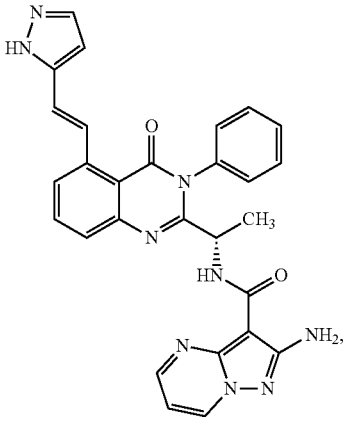
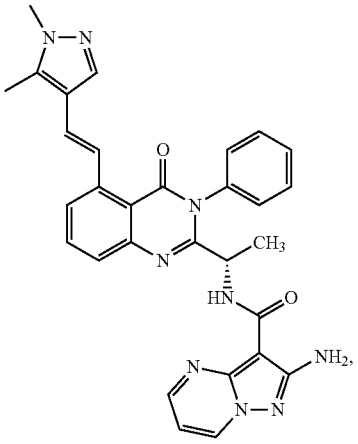
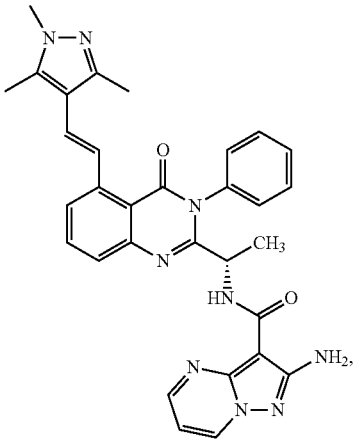


TABLE 6-continued

Compound 3007



Compound 3008



Compound 3009

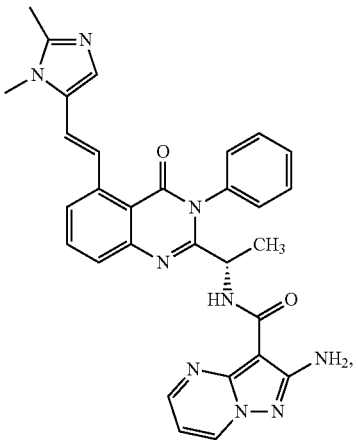
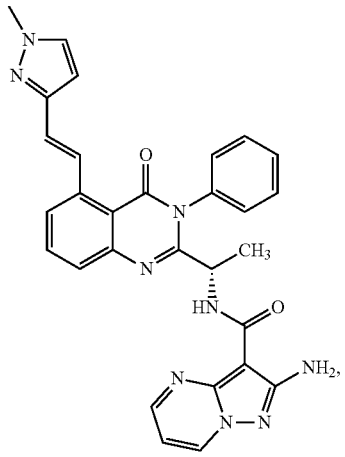
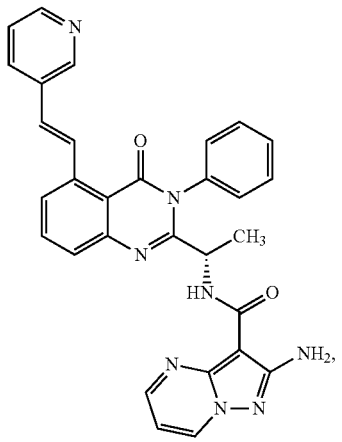


TABLE 6-continued

Compound 3010



Compound 3011



Compound 3012

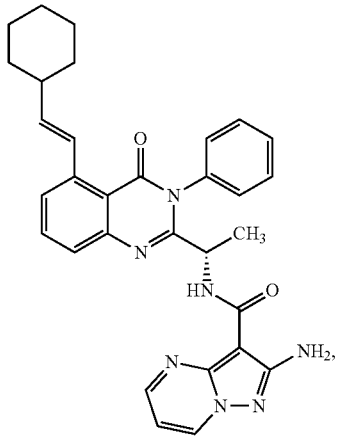
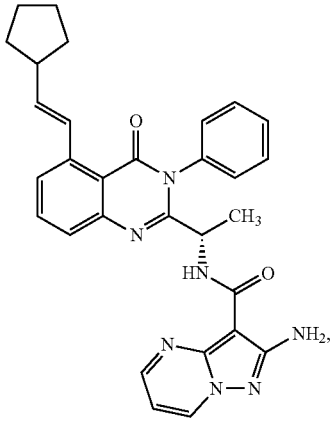
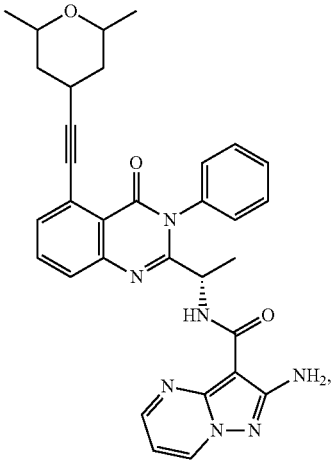


TABLE 6-continued

Compound 3013



Compound 3014



Compound 3015

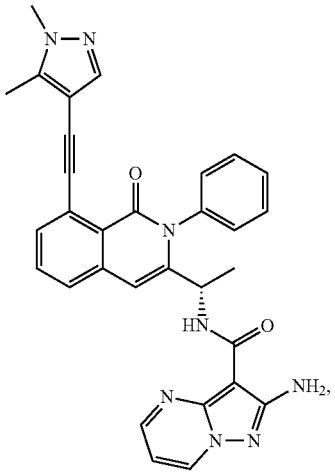


TABLE 6-continued

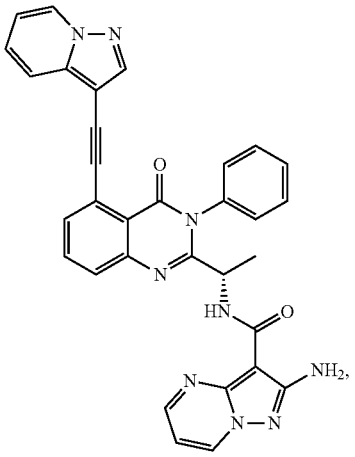
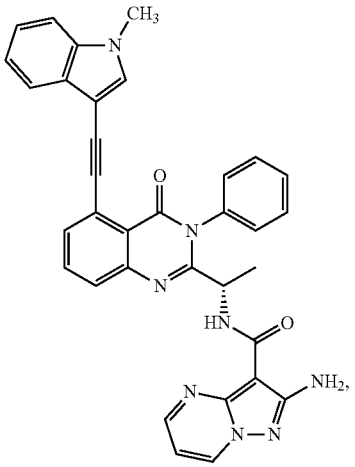
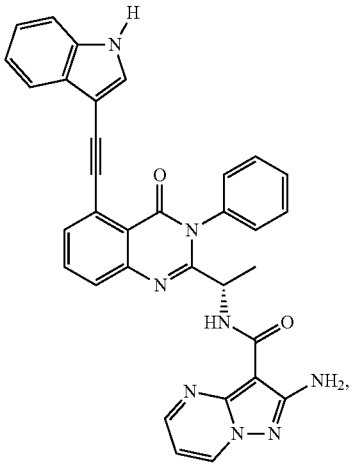
Compound 3016	
Compound 3017	
Compound 3018	

TABLE 6-continued

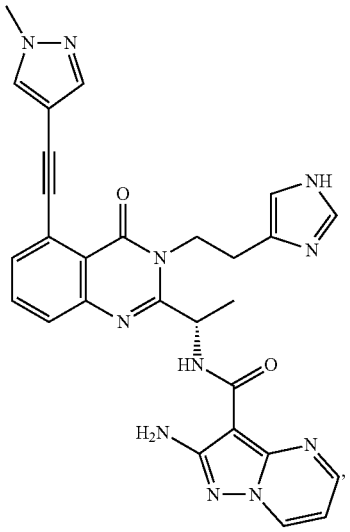
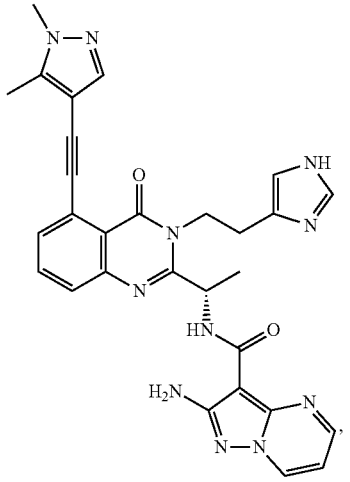
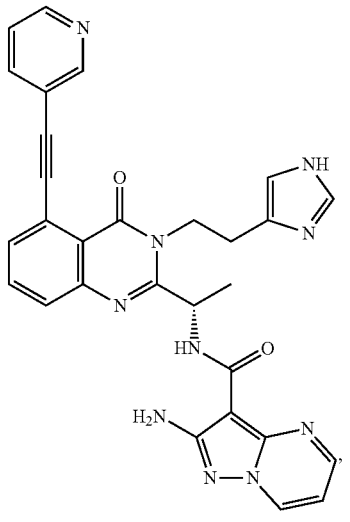
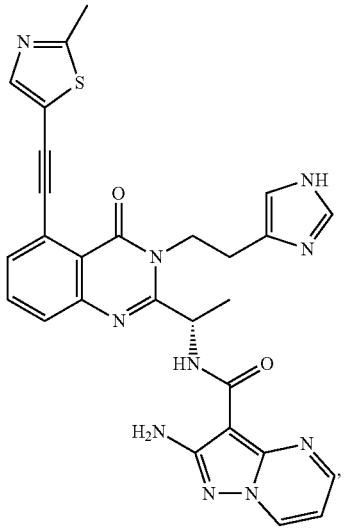
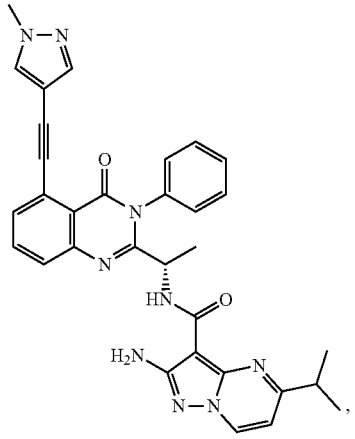
Compound 3045	
Compound 3046	
Compound 3047	

TABLE 6-continued

Compound 3048



Compound 3049



Compound 3050

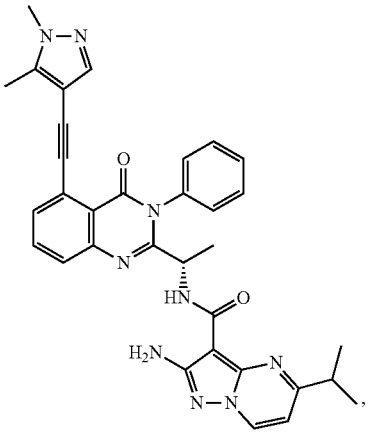
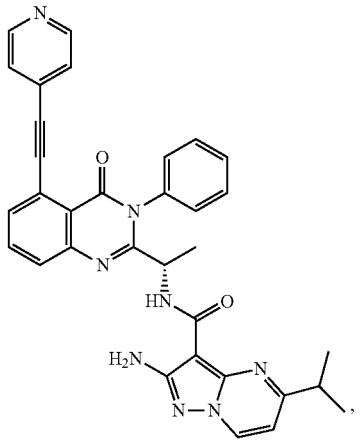
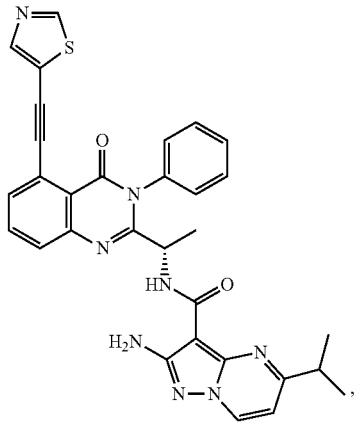


TABLE 6-continued

Compound 3051



Compound 3052



Compound 3053

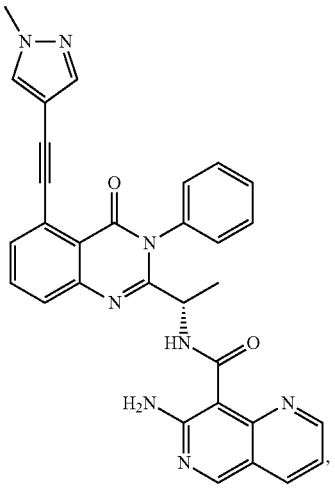
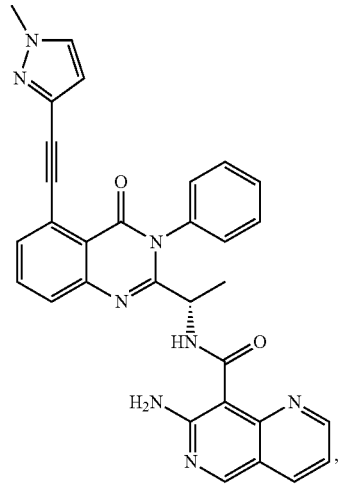
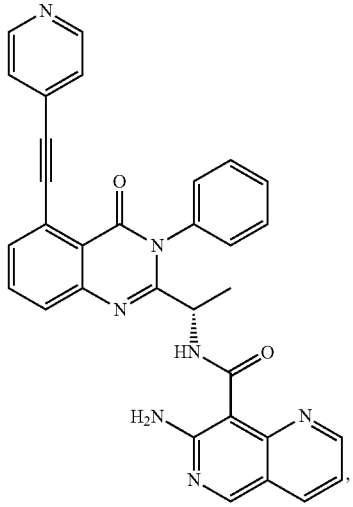


TABLE 6-continued

Compound 3054



Compound 3055



Compound 3056

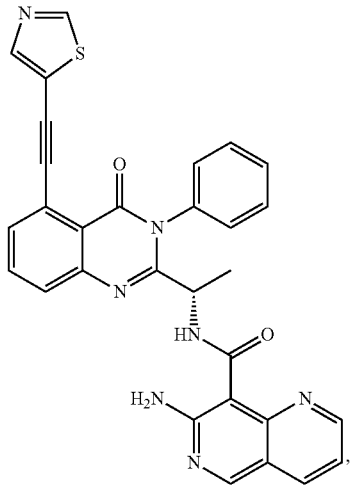
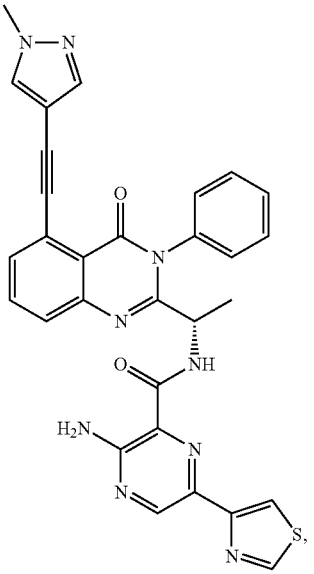


TABLE 6-continued

Compound 3057



Compound 3058

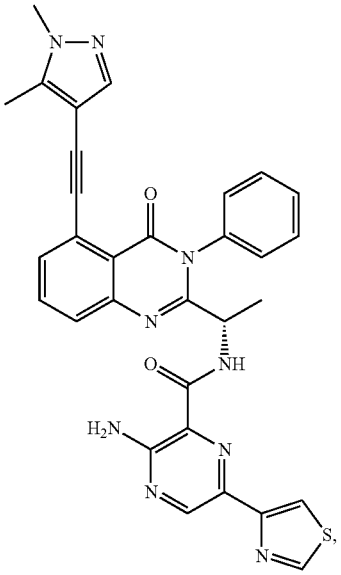
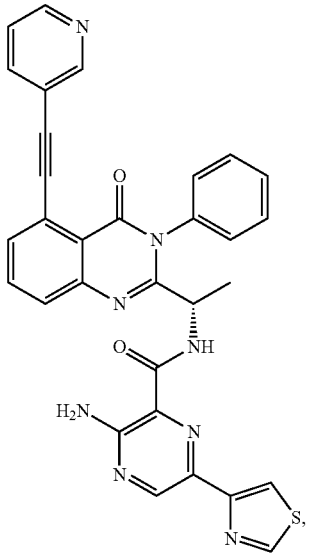
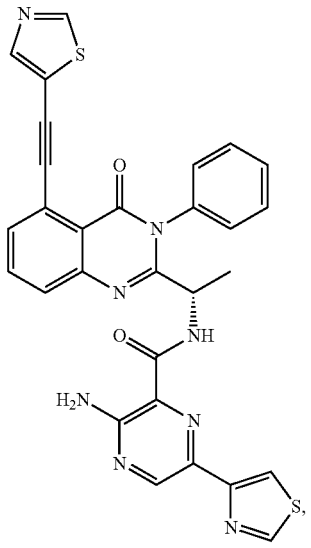


TABLE 6-continued

Compound 3059



Compound 3060



Compound 3061

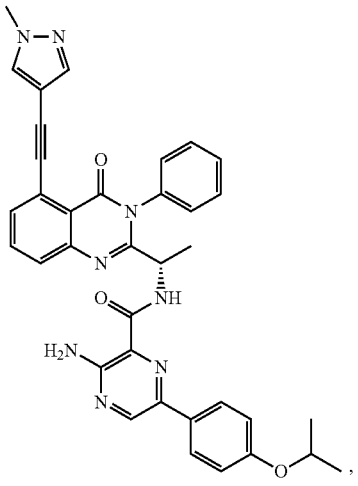
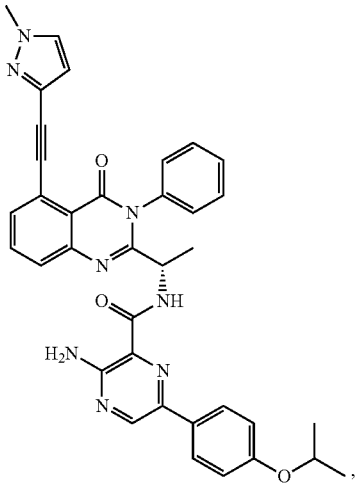
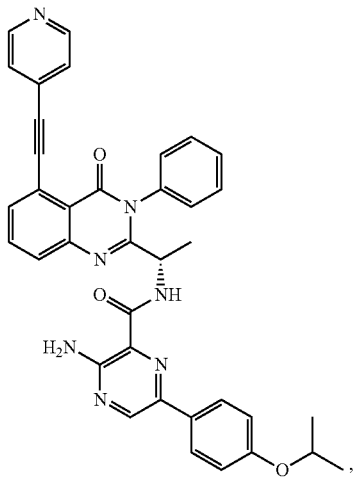


TABLE 6-continued

Compound 3062



Compound 3063



Compound 3064

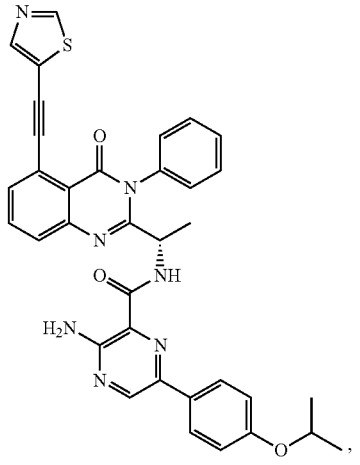
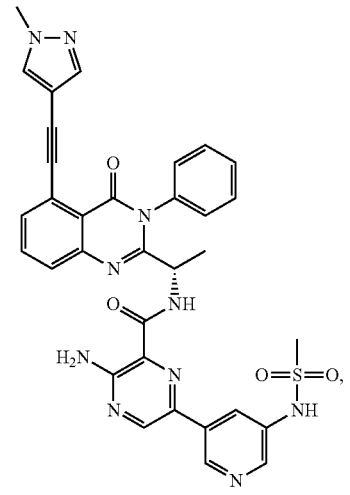
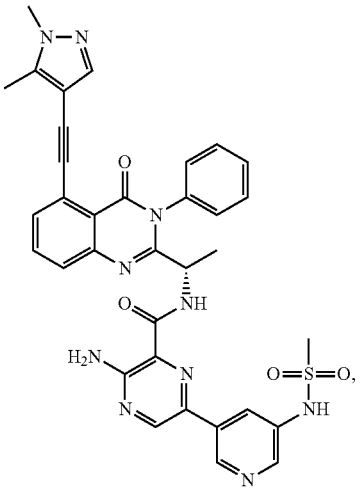


TABLE 6-continued

Compound 3065



Compound 3066



Compound 3067

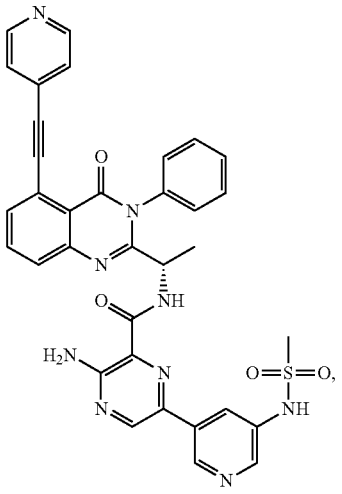
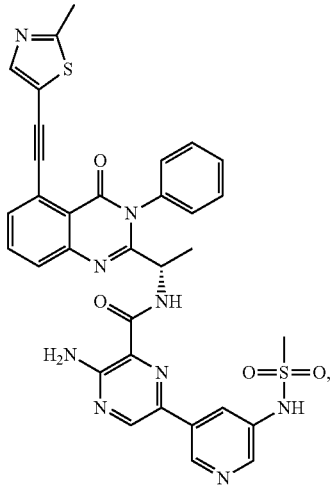
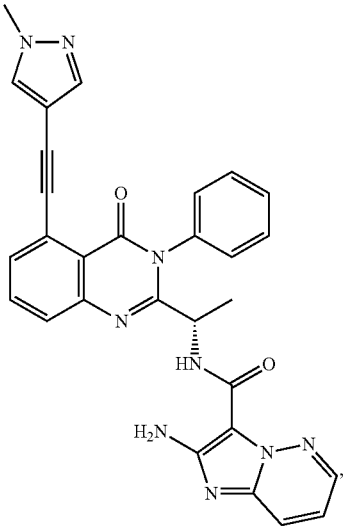


TABLE 6-continued

Compound 3068



Compound 3069



Compound 3070

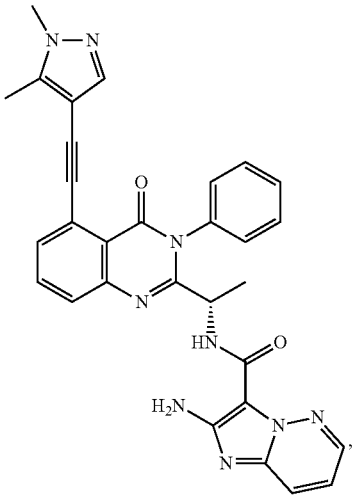
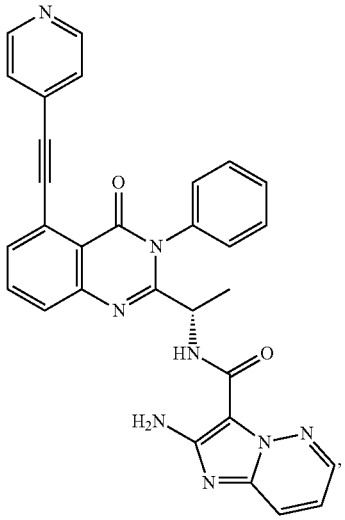
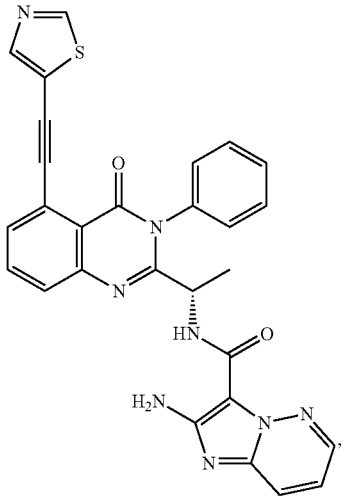


TABLE 6-continued

Compound 3071



Compound 3072



Compound 3073

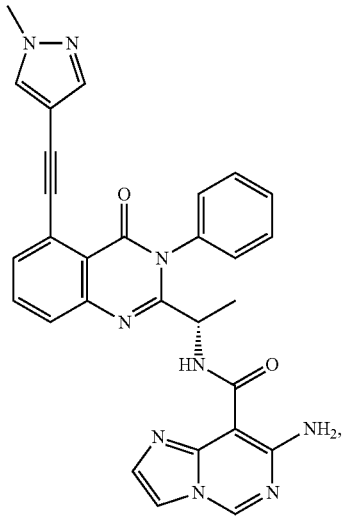
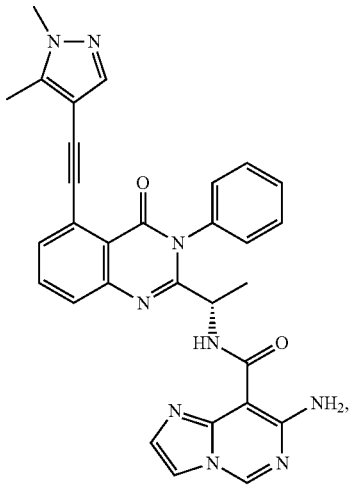
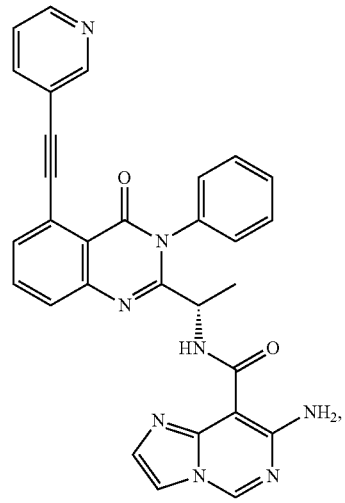


TABLE 6-continued

Compound 3074



Compound 3075



Compound 3076

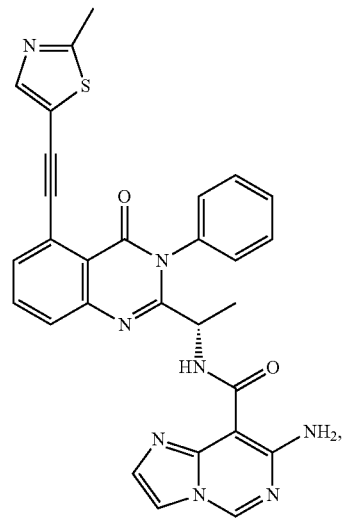


TABLE 6-continued

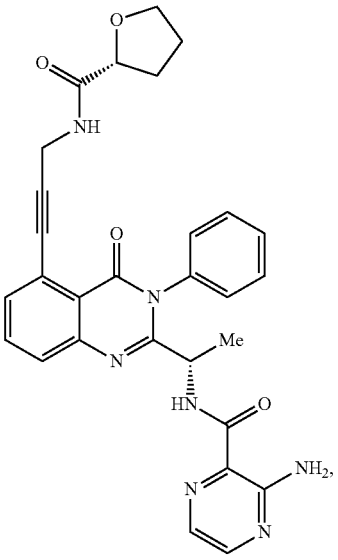
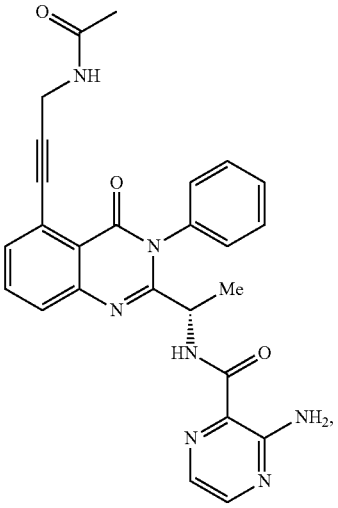
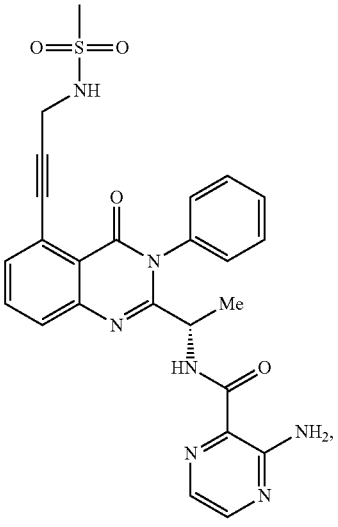
Compound 3077	
Compound 3078	
Compound 3079	

TABLE 6-continued

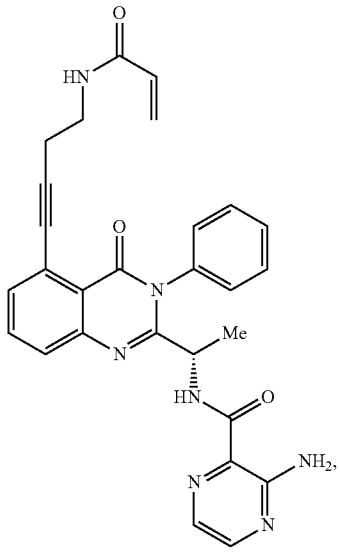
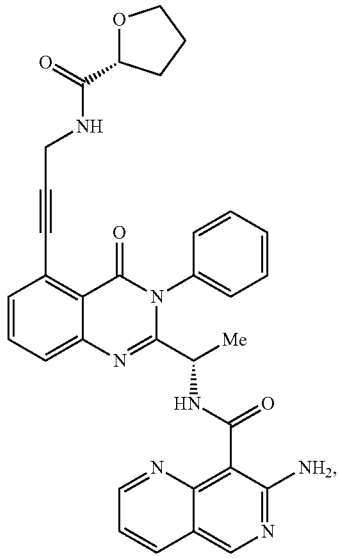
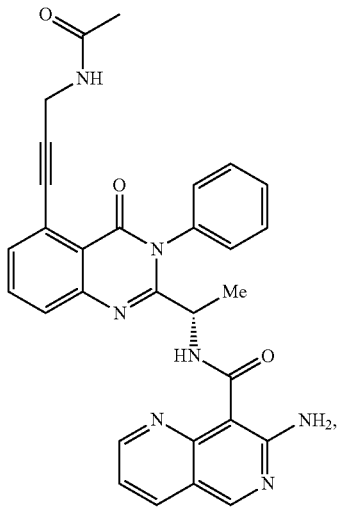
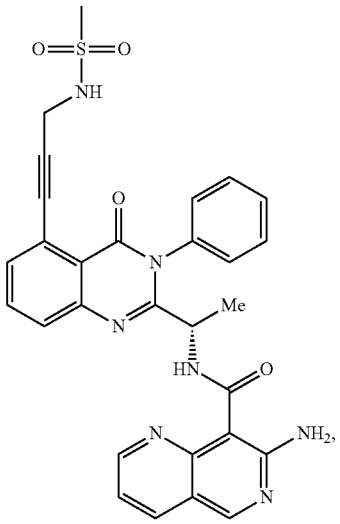
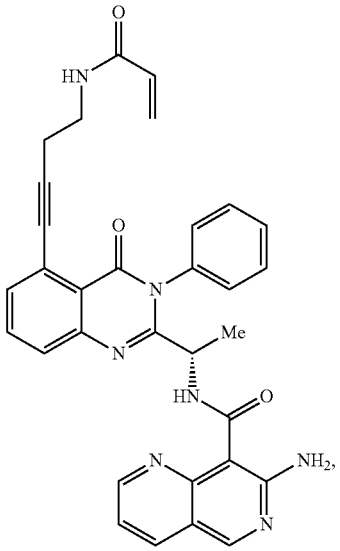
Compound 3080	
Compound 3081	
Compound 3082	

TABLE 6-continued

Compound 3083



Compound 3084



Compound 3085

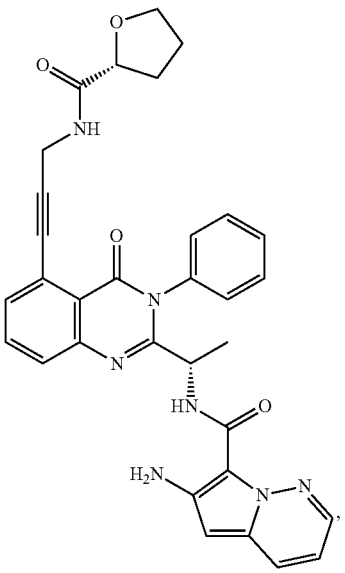
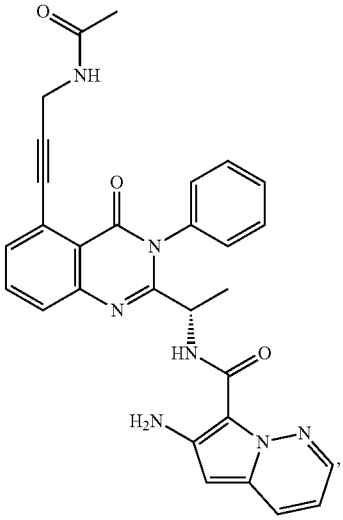
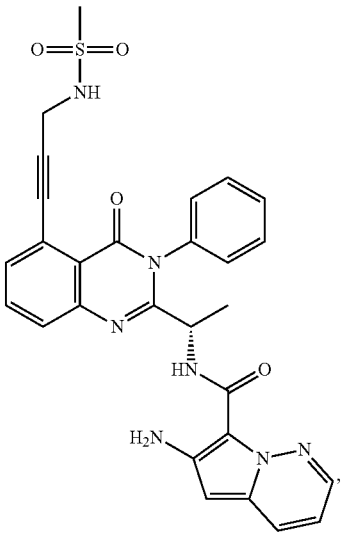


TABLE 6-continued

Compound 3086



Compound 3087



Compound 3088

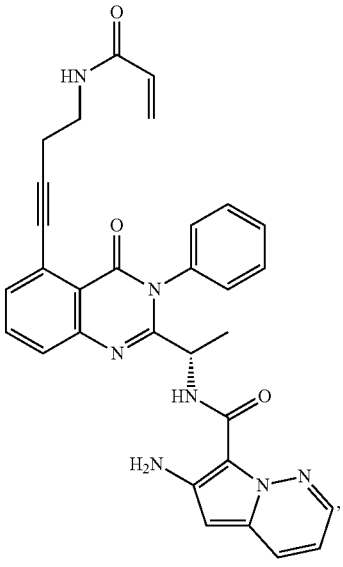
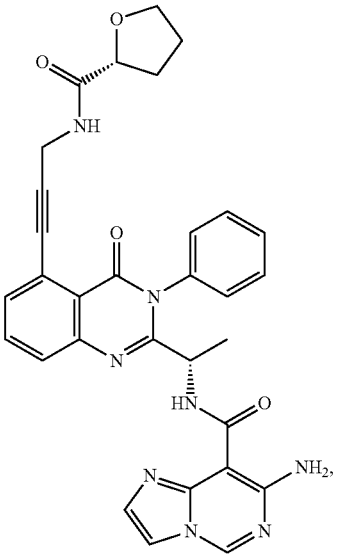
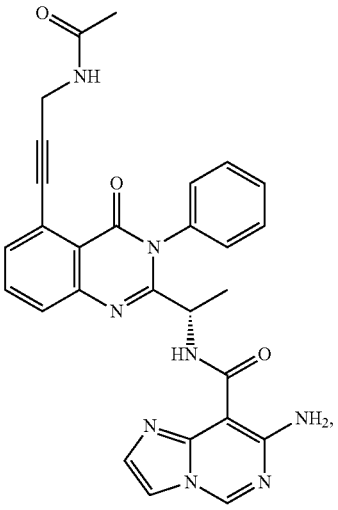


TABLE 6-continued

Compound 3089



Compound 3090



Compound 3091

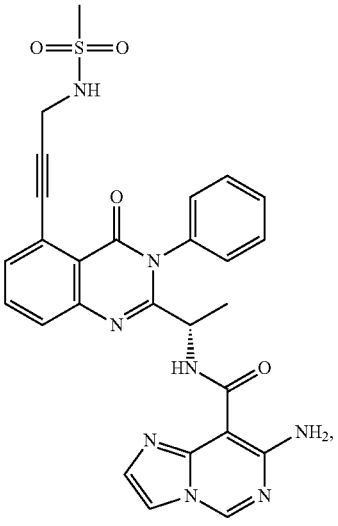


TABLE 6-continued

Compound 3092

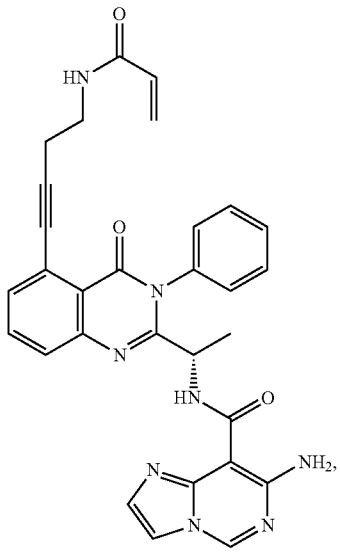
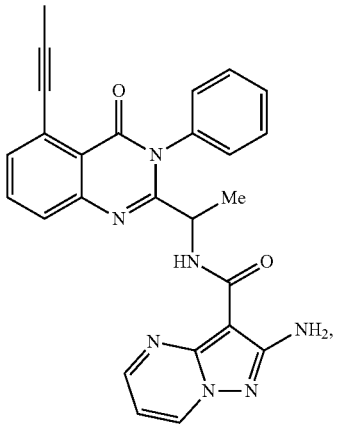


TABLE 7

Compound 1'



Compound 2'

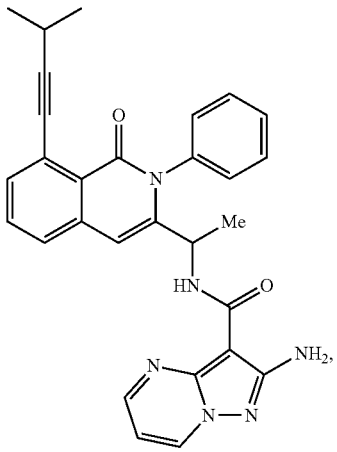


TABLE 7-continued

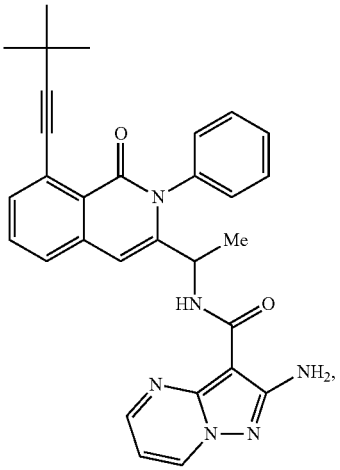
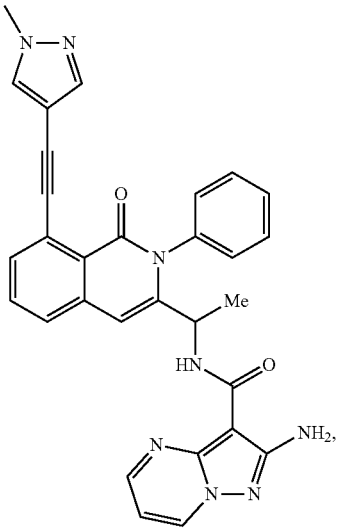
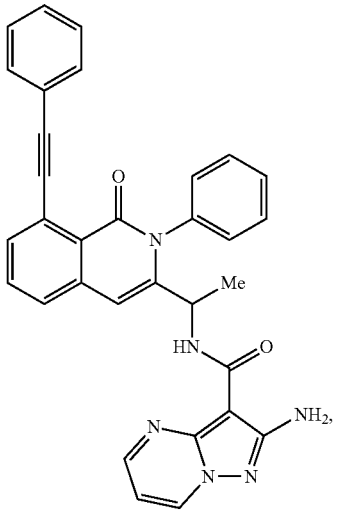
Compound 3'	
Compound 4'	
Compound 5'	

TABLE 7-continued

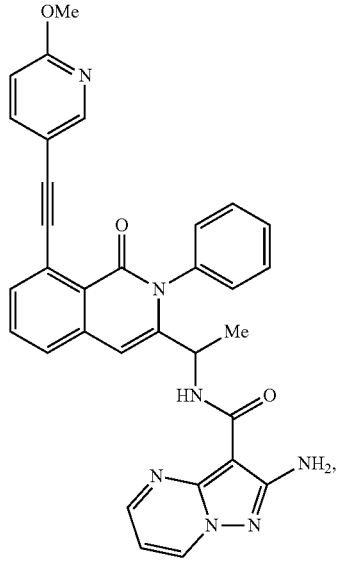
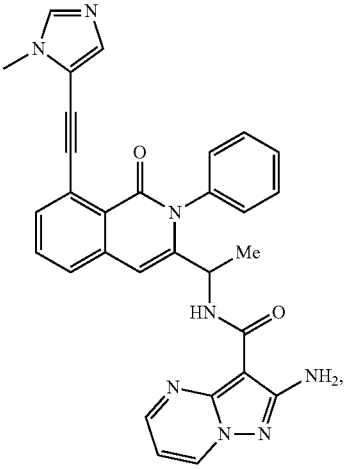
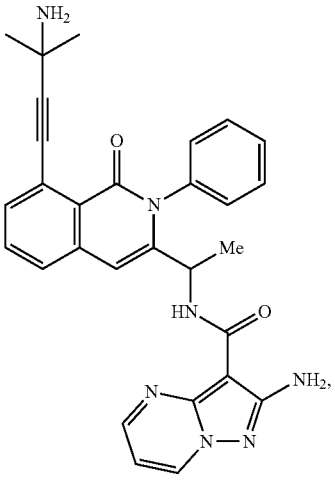
Compound 6'	
Compound 7'	
Compound 8'	

TABLE 7-continued

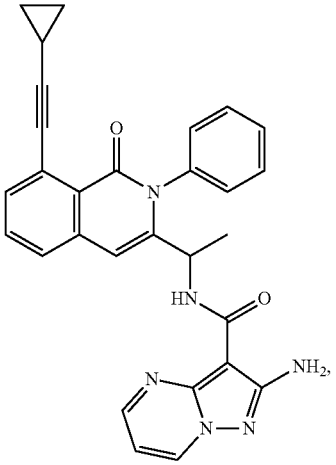
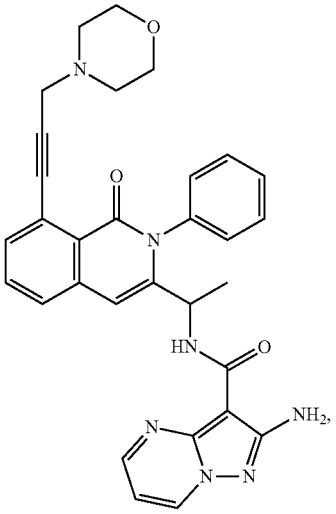
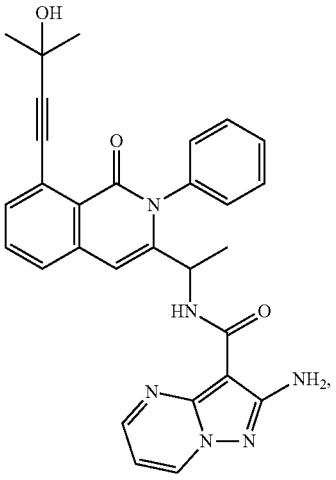
Compound 9'	
Compound 10'	
Compound 11'	

TABLE 7-continued

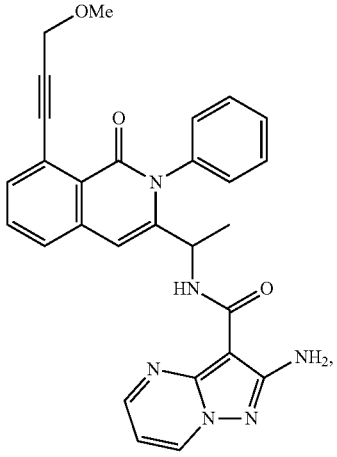
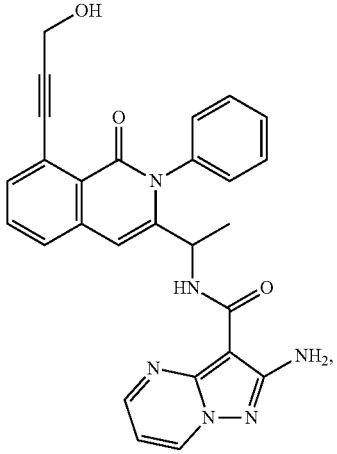
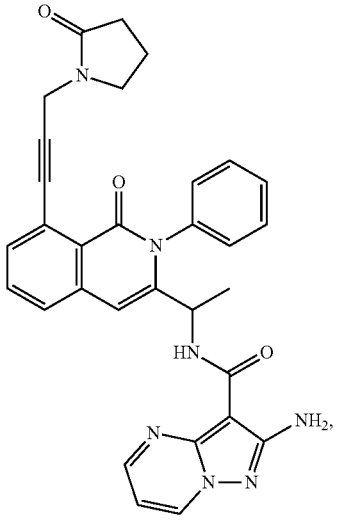
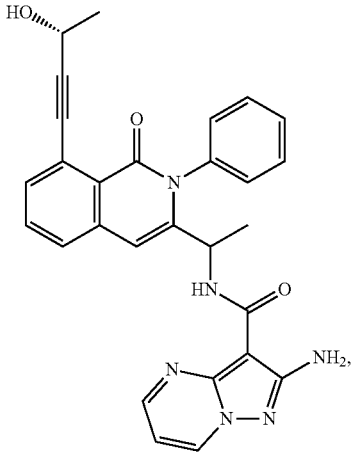
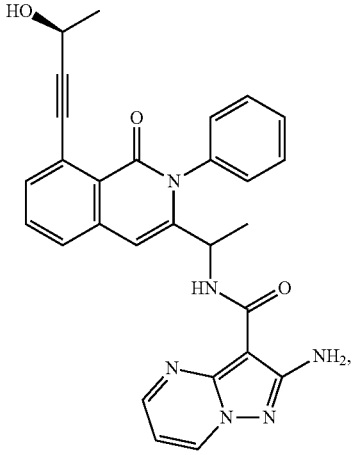
Compound 12'	
Compound 13'	
Compound 14'	

TABLE 7-continued

Compound 15'



Compound 16'



Compound 17'

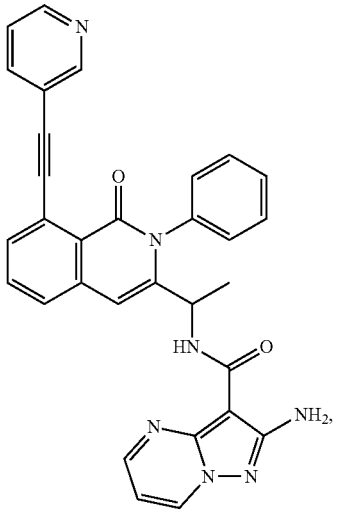
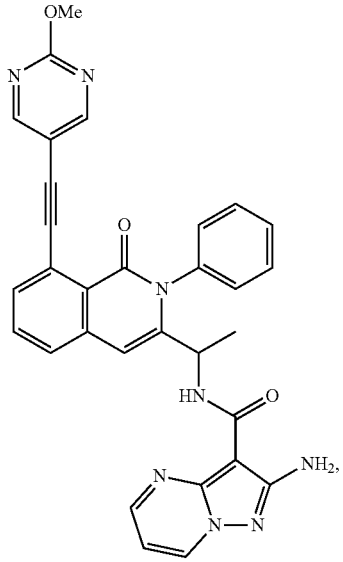
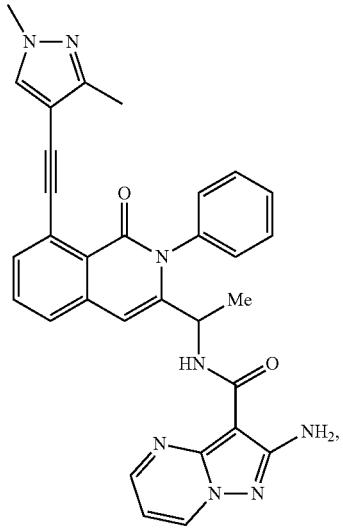


TABLE 7-continued

Compound 18'



Compound 19'



Compound 20'

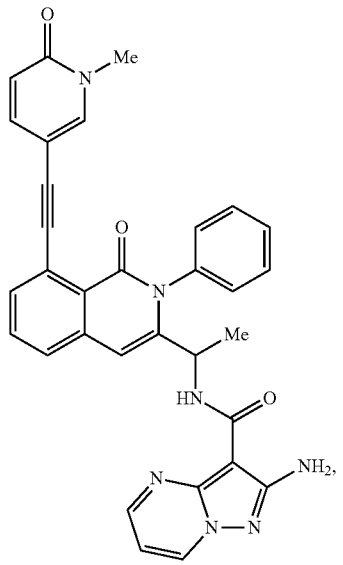
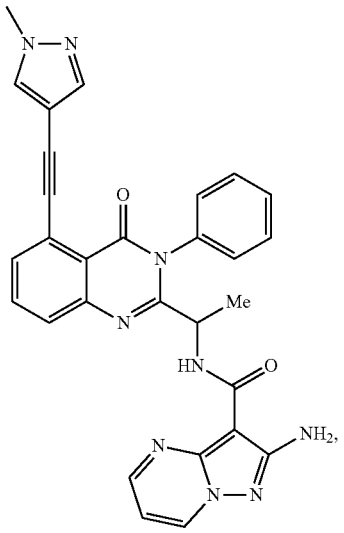
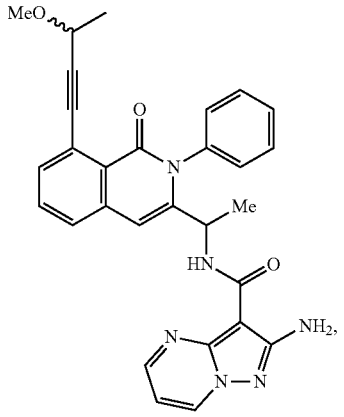


TABLE 7-continued

Compound 21'



Compound 22'



Compound 23'

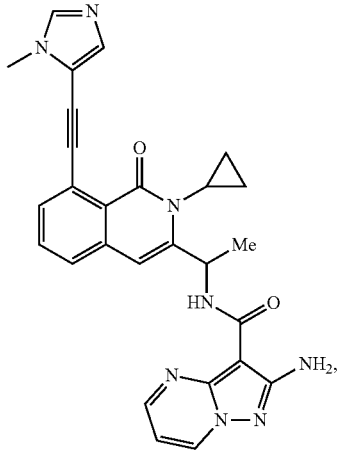
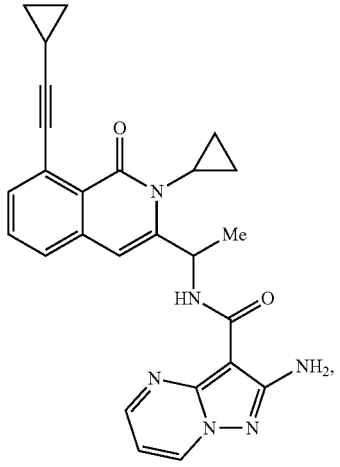
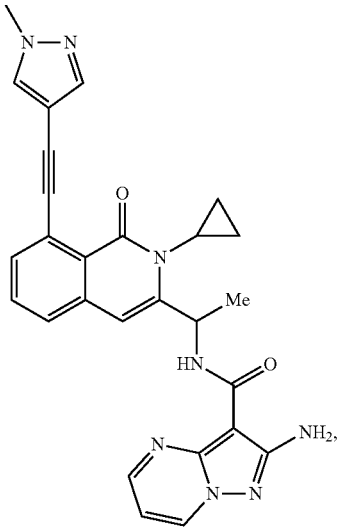


TABLE 7-continued

Compound 24'



Compound 25'



Compound 26'

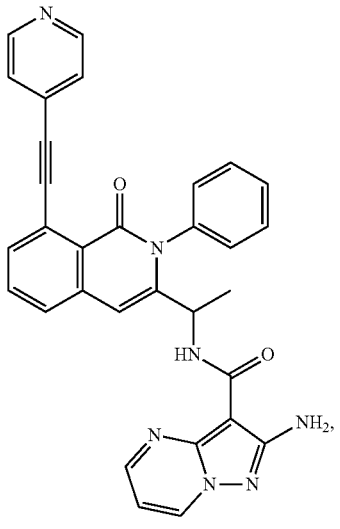


TABLE 7-continued

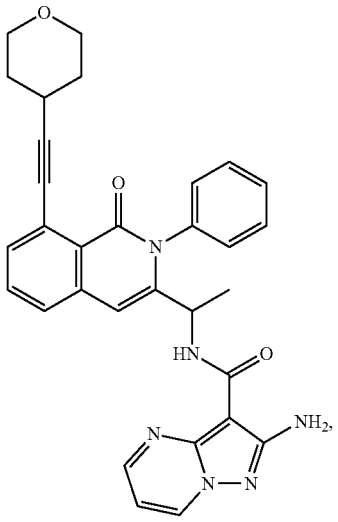
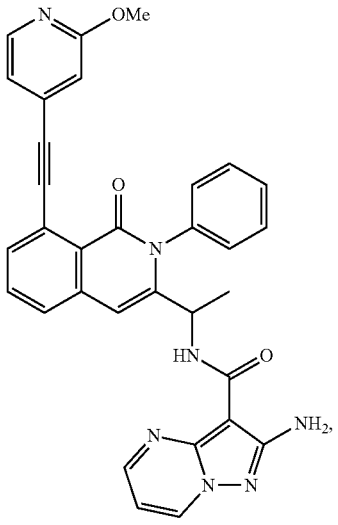
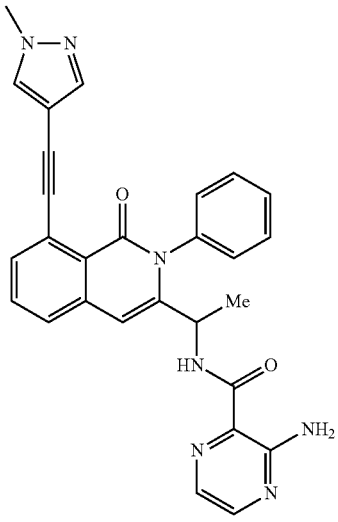
Compound 27'	
Compound 28'	
Compound 29'	

TABLE 7-continued

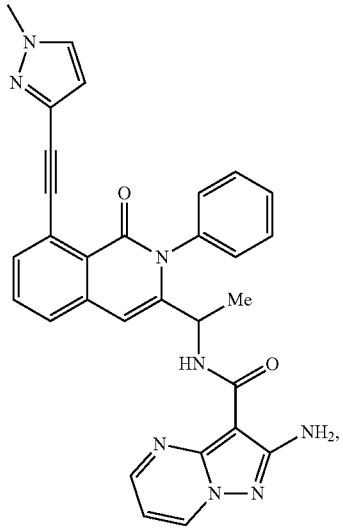
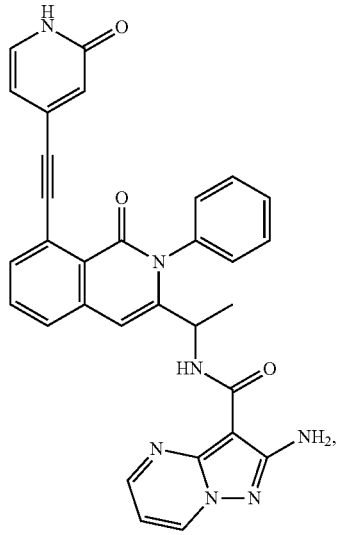
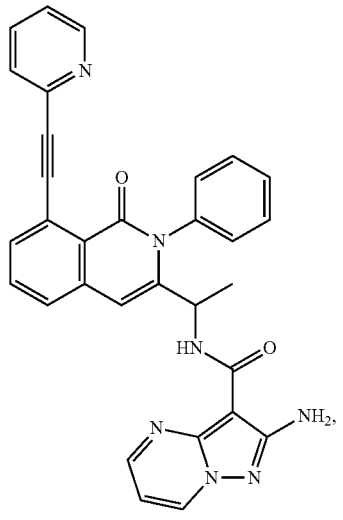
Compound 30'	
Compound 31'	
Compound 32'	

TABLE 7-continued

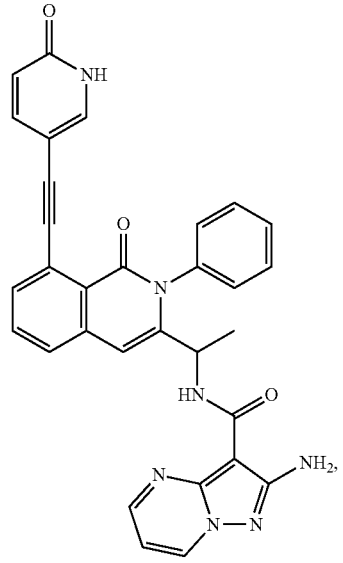
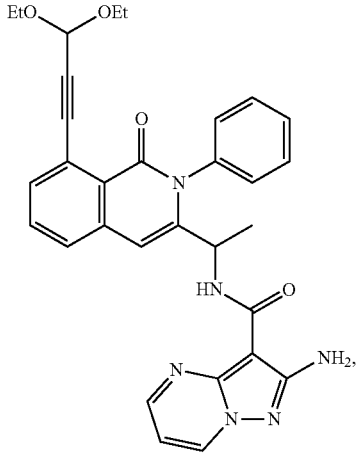
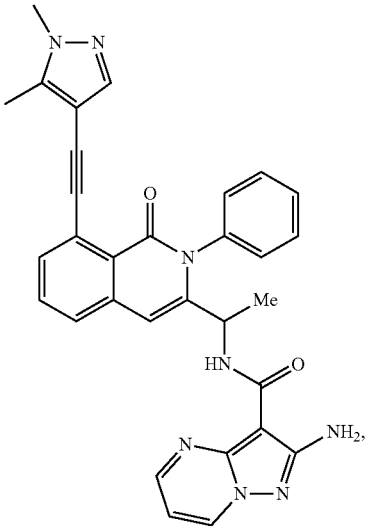
Compound 33'	
Compound 34'	
Compound 35'	

TABLE 7-continued

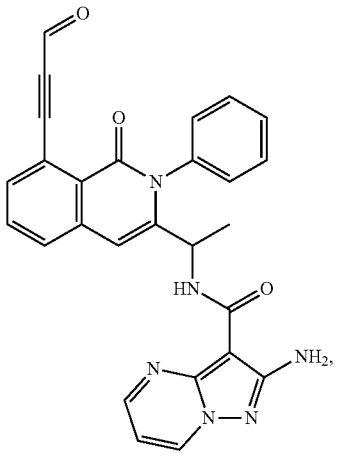
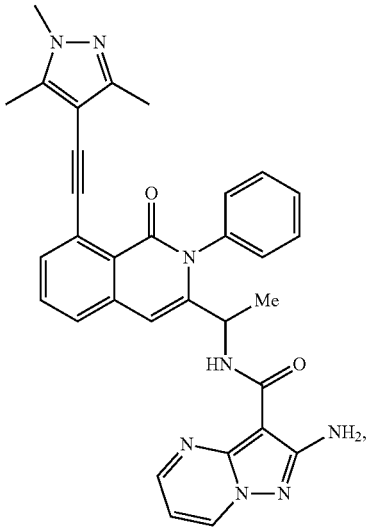
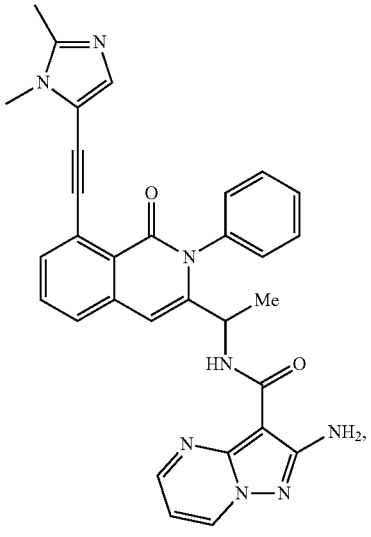
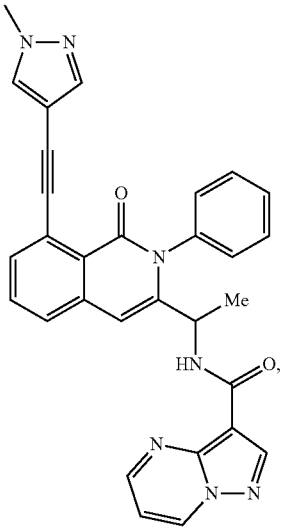
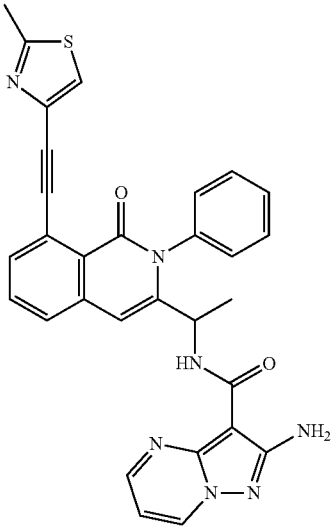
Compound 36A'	
Compound 37'	
Compound 38'	

TABLE 7-continued

Compound 39'



Compound 40'



Compound 41'

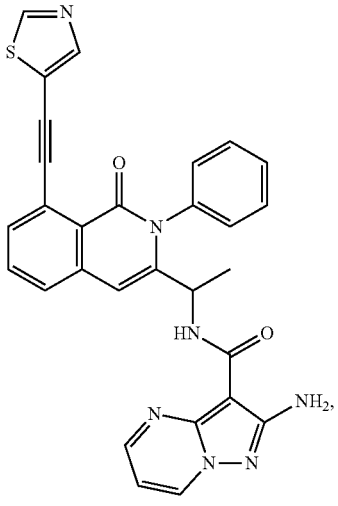
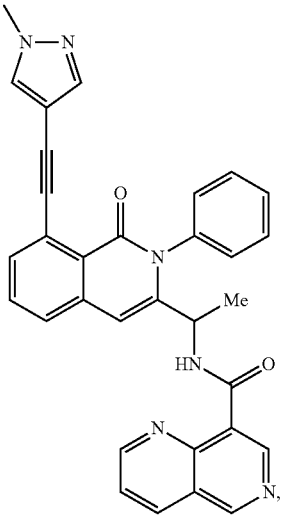
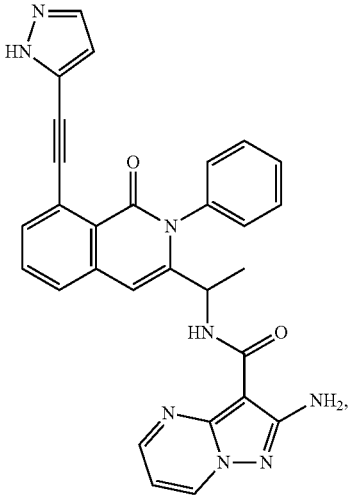


TABLE 7-continued

Compound 42'



Compound 43'



Compound 44'

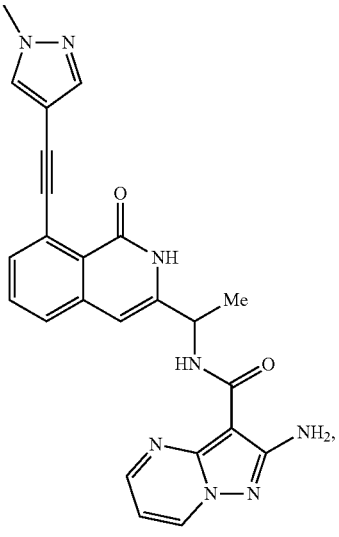
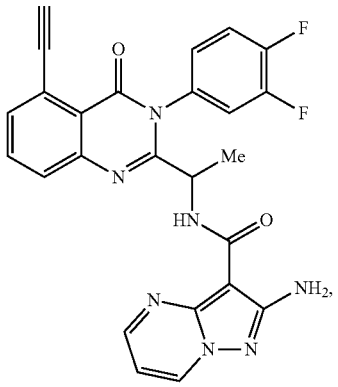
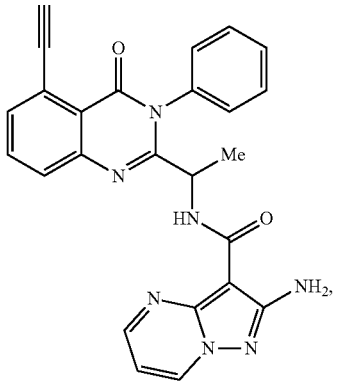


TABLE 7-continued

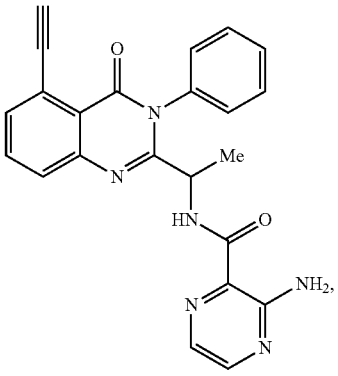
Compound 45'



Compound 46'



Compound 47'



Compound 48'

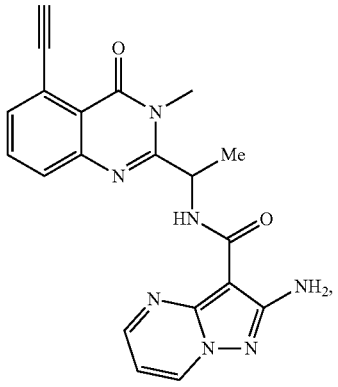
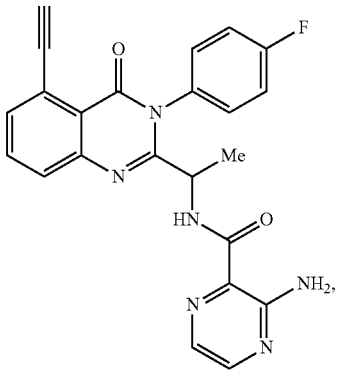
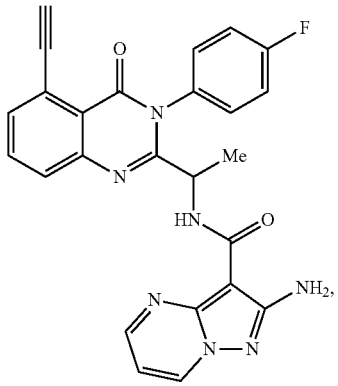


TABLE 7-continued

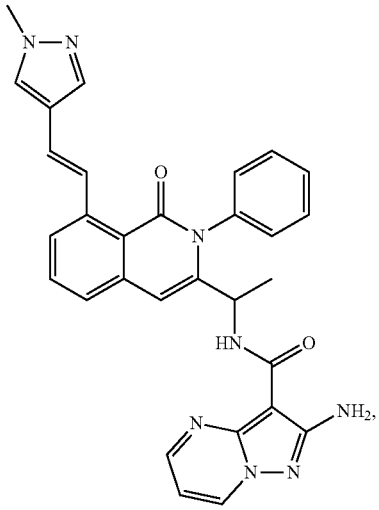
Compound 49'



Compound 50'



Compound 52'



Compound 53'

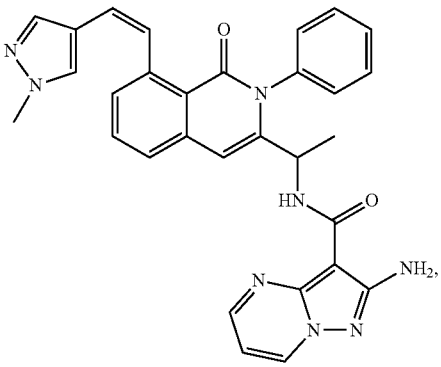
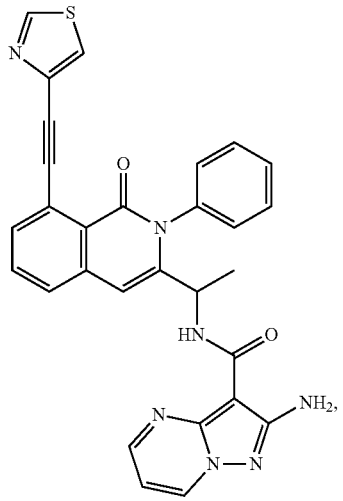
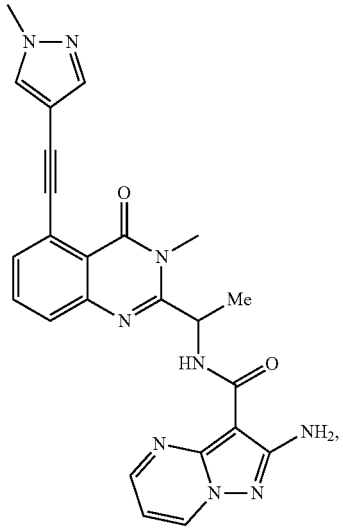


TABLE 7-continued

Compound 54'



Compound 55'



Compound 56'

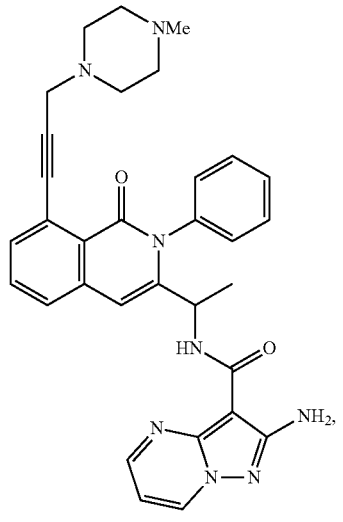
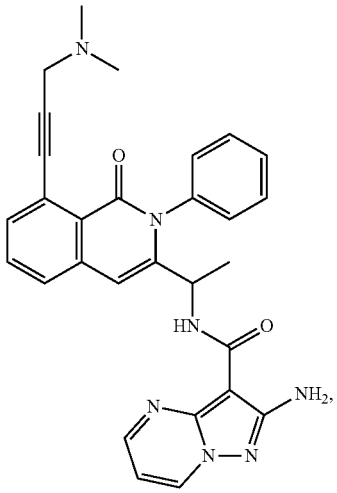
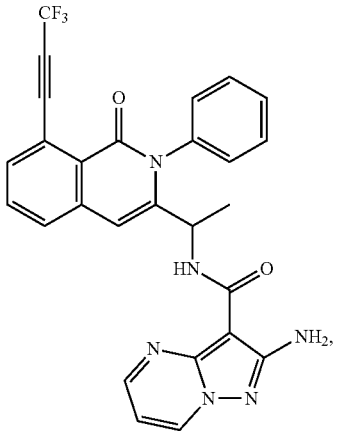


TABLE 7-continued

Compound 57'



Compound 58'



Compound 59'

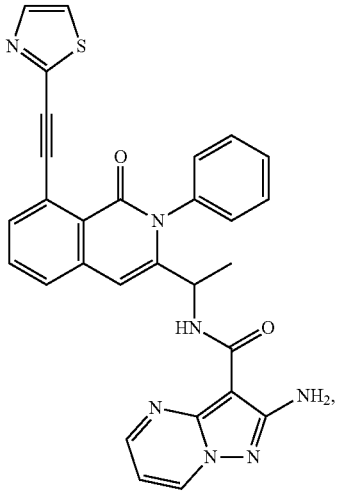
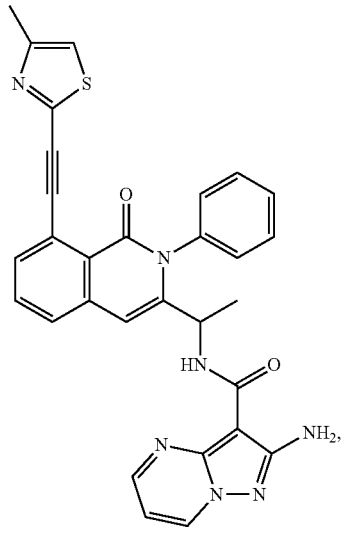
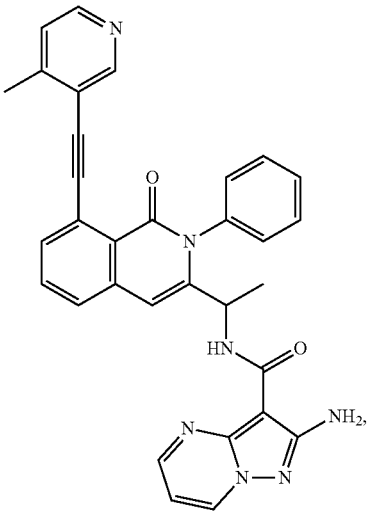


TABLE 7-continued

Compound 60'



Compound 61'



Compound 62'

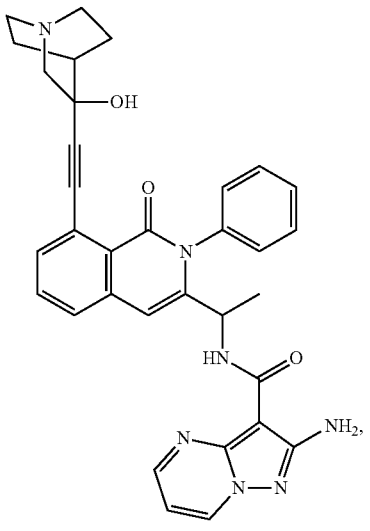
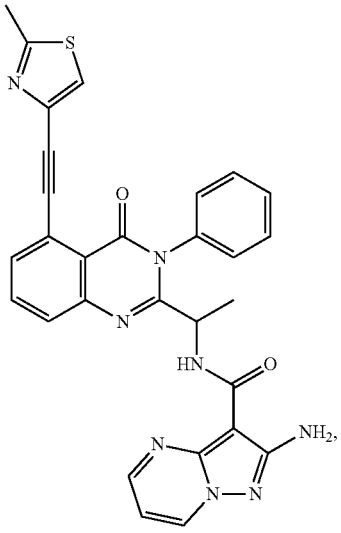
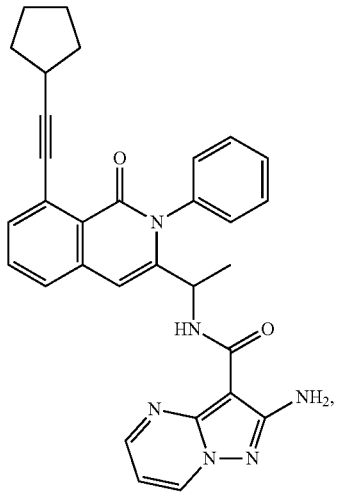


TABLE 7-continued

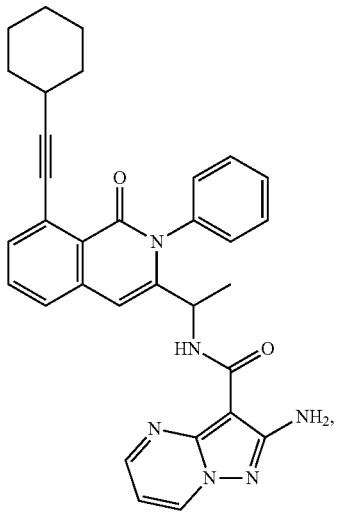
Compound 63'



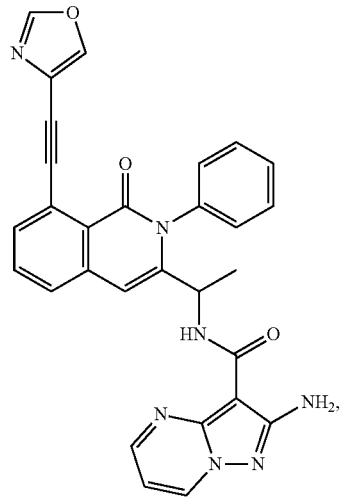
Compound 64'



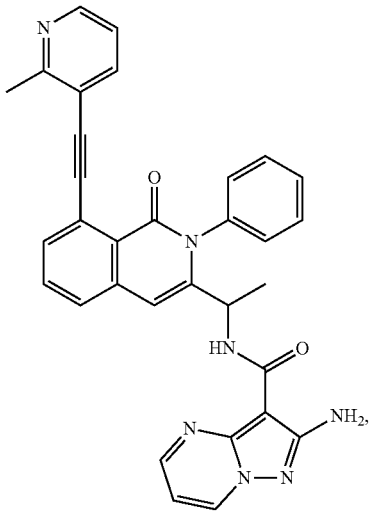
Compound 65'



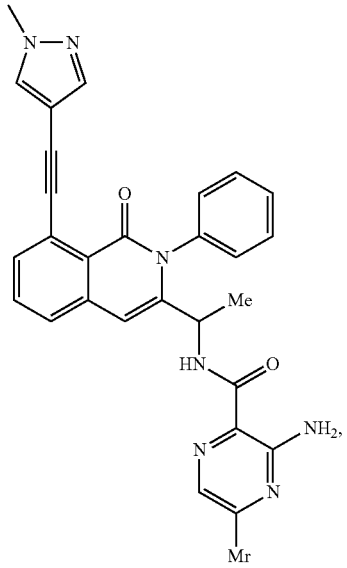
Compound 66'



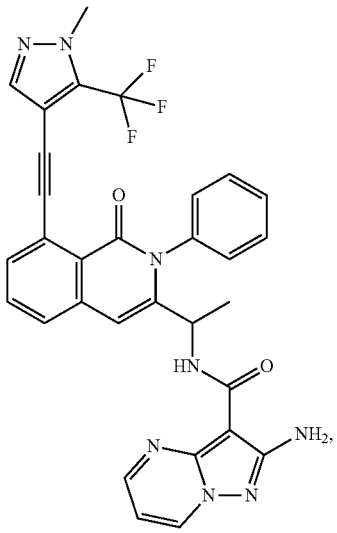
Compound 67'



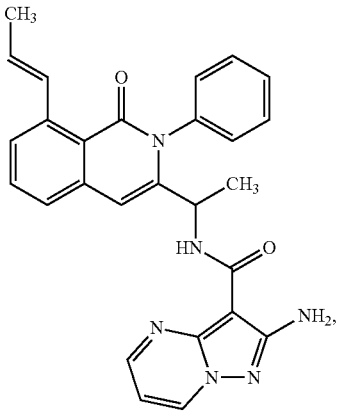
Compound 68'



Compound 69'



Compound 70'



Compound 71'

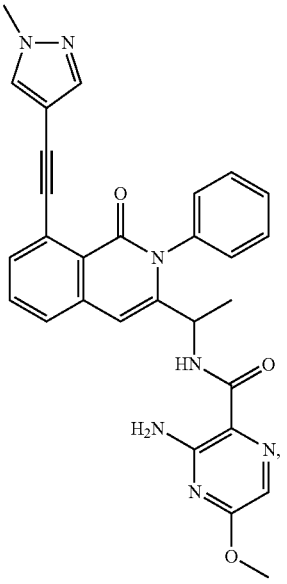


TABLE 7-continued

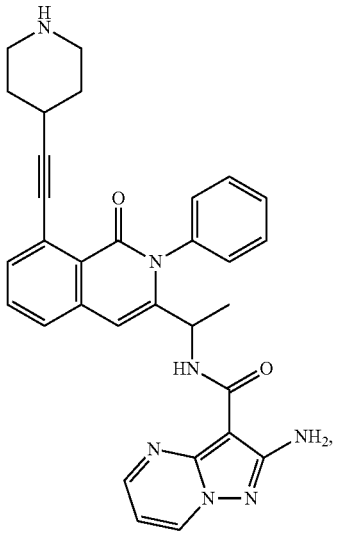
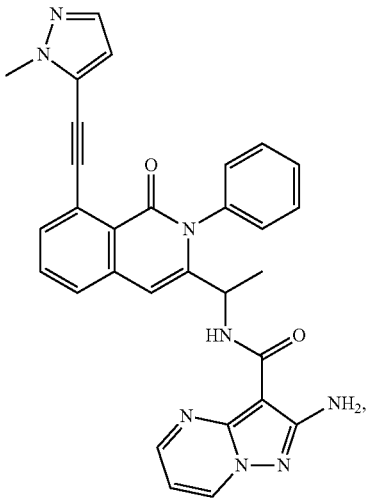
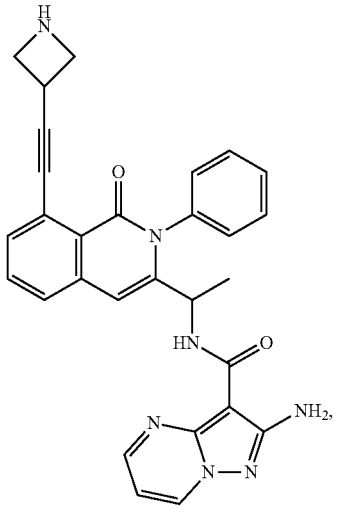
Compound 72'	
Compound 73'	
Compound 74'	

TABLE 7-continued

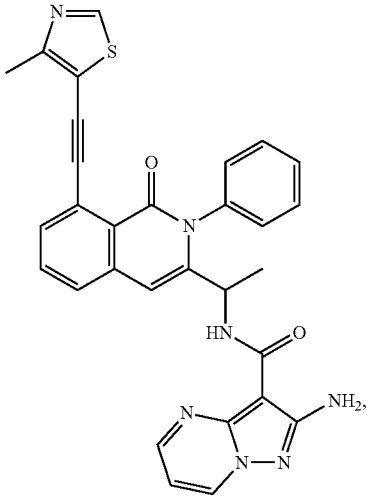
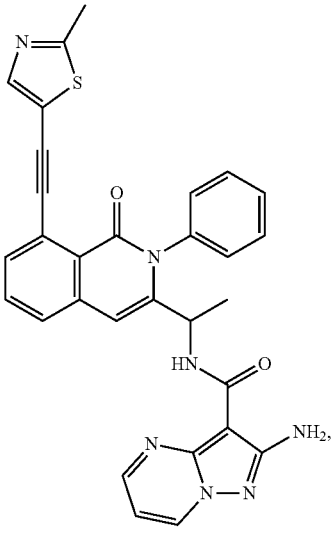
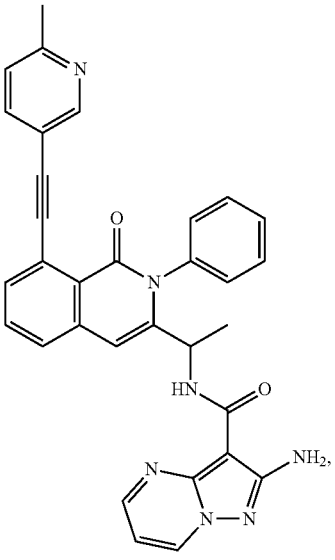
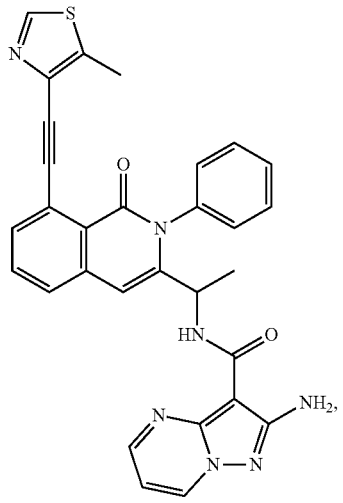
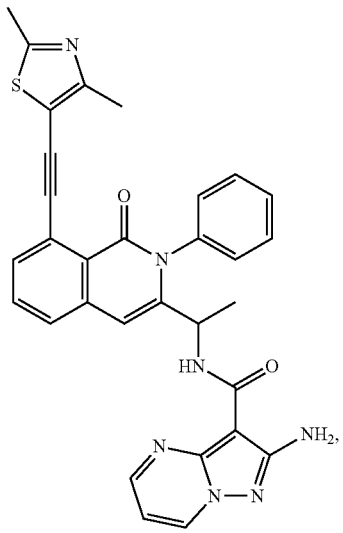
Compound 75'	
Compound 76'	
Compound 77'	

TABLE 7-continued

Compound 78'



Compound 79'



Compound 80'

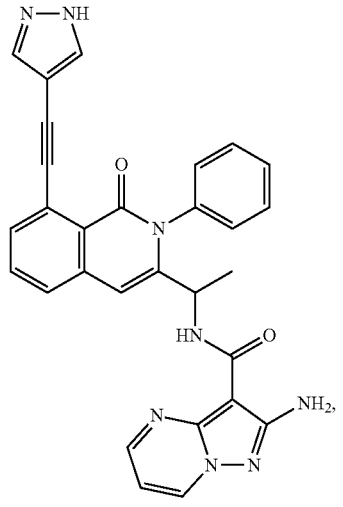
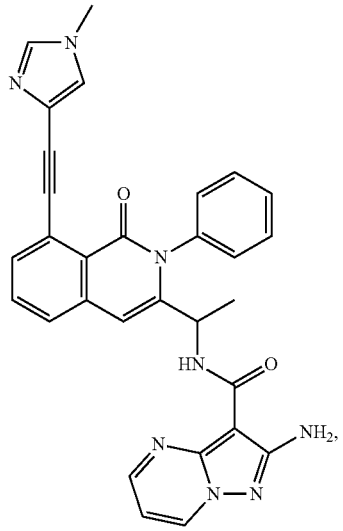


TABLE 7-continued

Compound 81'



Compound 82'

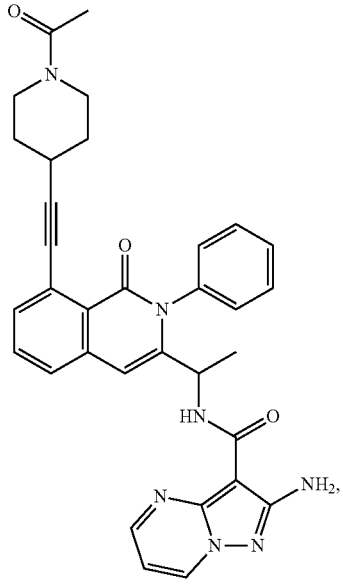
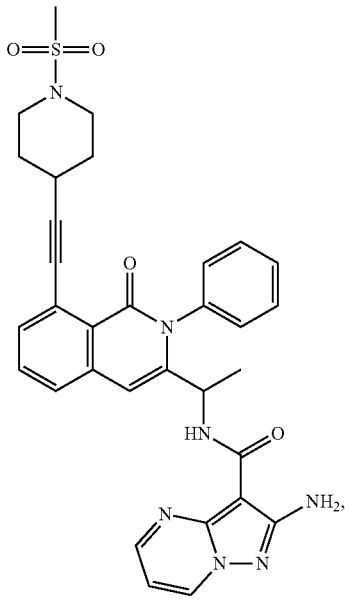
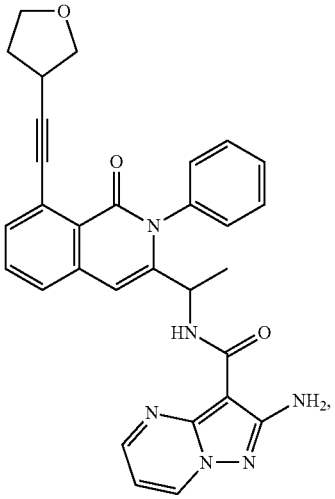


TABLE 7-continued

Compound 83'



Compound 84'



Compound 85'

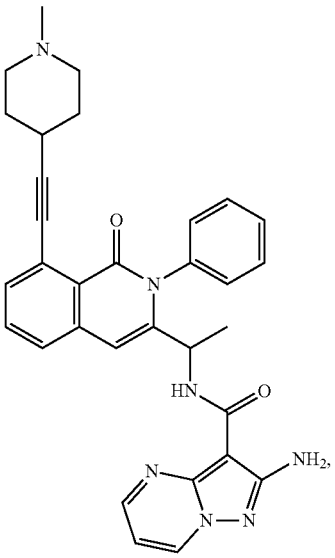
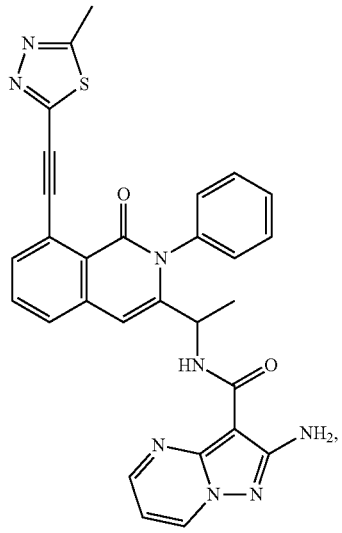
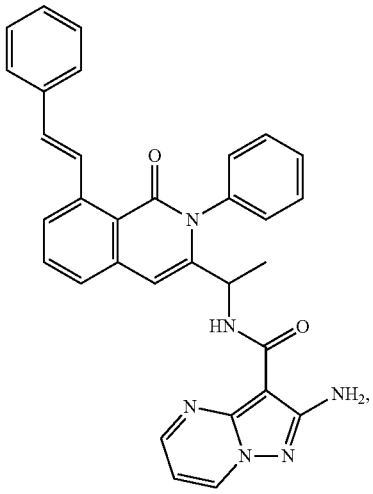


TABLE 7-continued

Compound 86'



Compound 87'



Compound 88'

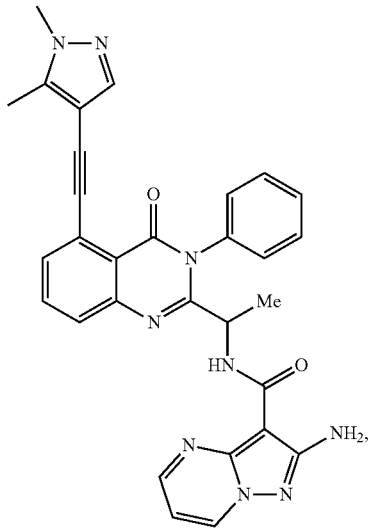
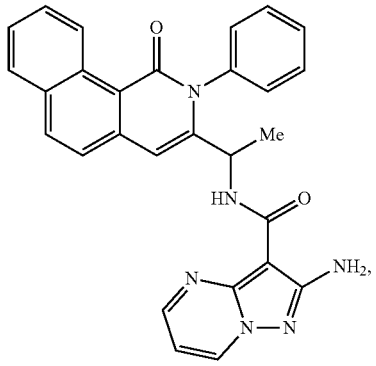
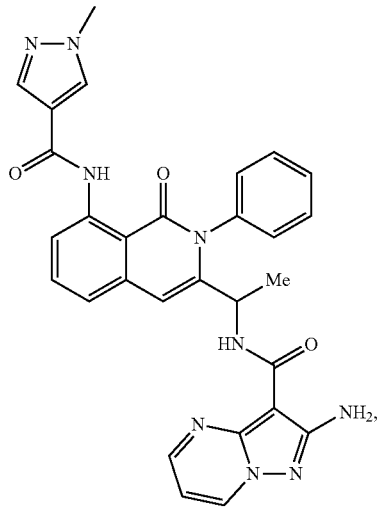


TABLE 7-continued

Compound 89'



Compound 90'



Compound 91'

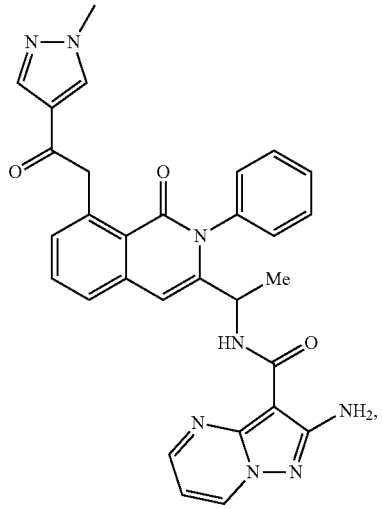
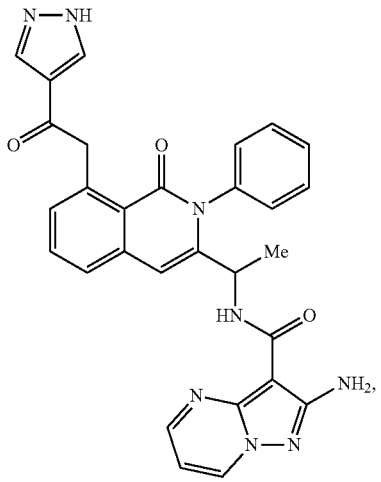
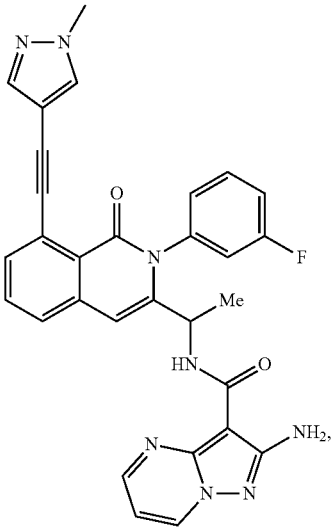


TABLE 7-continued

Compound 92'



Compound 93'



Compound 94'

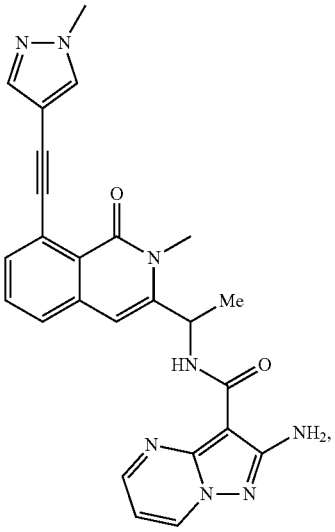
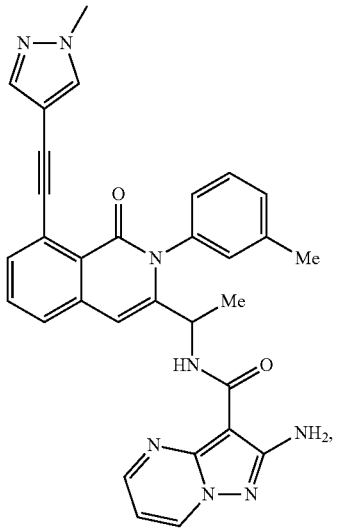
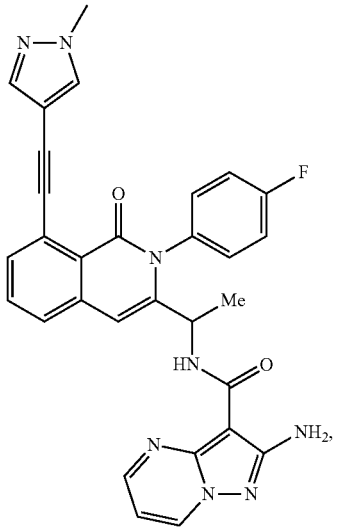


TABLE 7-continued

Compound 95'



Compound 96'



Compound 97'

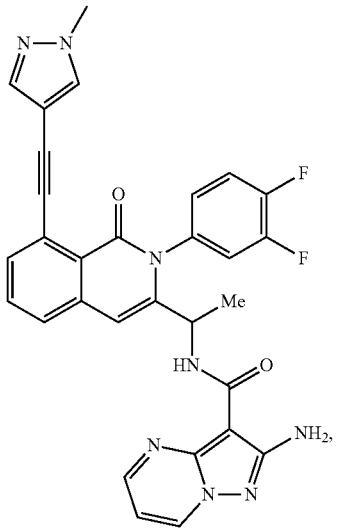
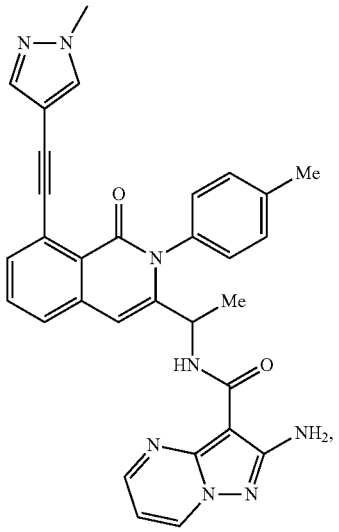
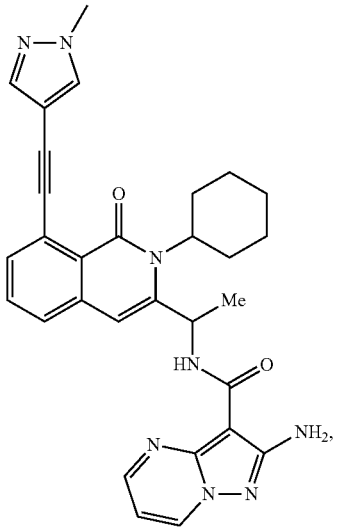


TABLE 7-continued

Compound 98'



Compound 99'



Compound 100'

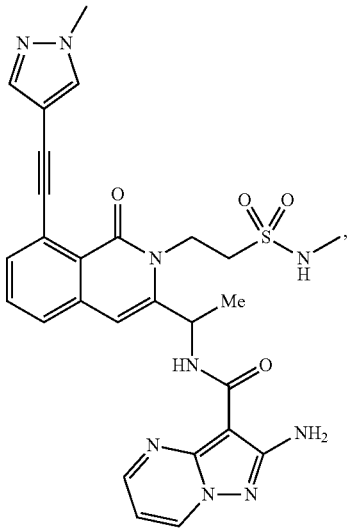
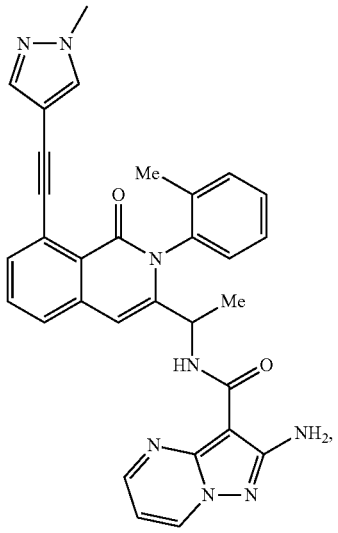
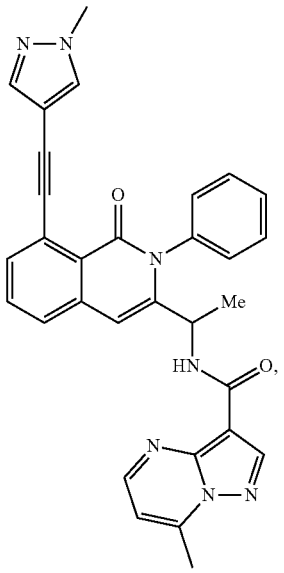


TABLE 7-continued

Compound 101'



Compound 102'



Compound 103'

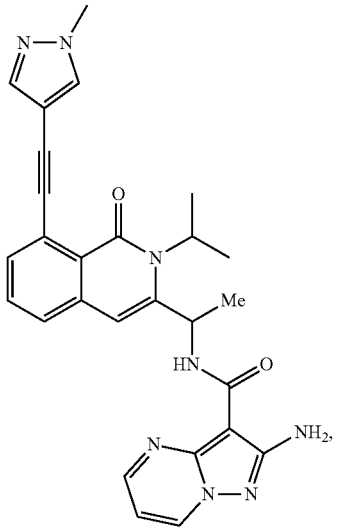
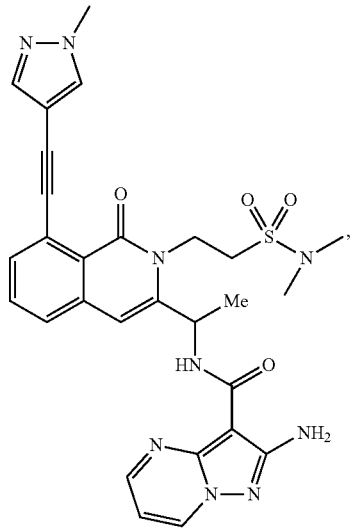
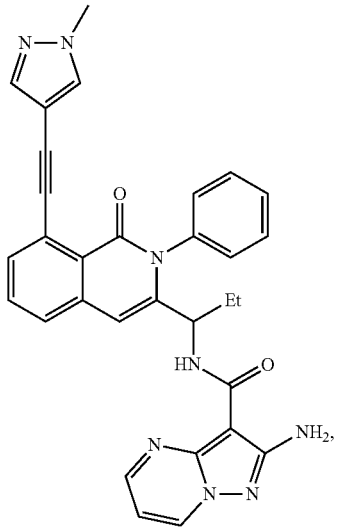


TABLE 7-continued

Compound 104'



Compound 105'



Compound 106'

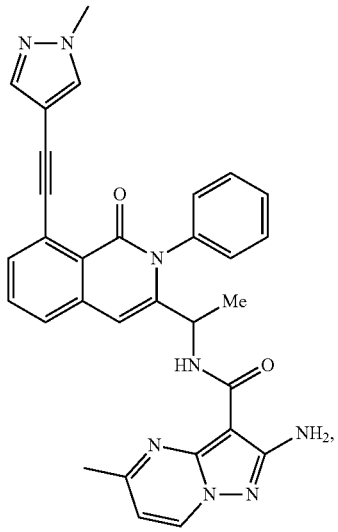
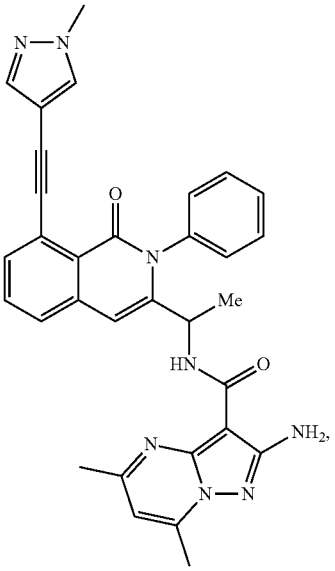


TABLE 7-continued

Compound 108'



Compound 109'

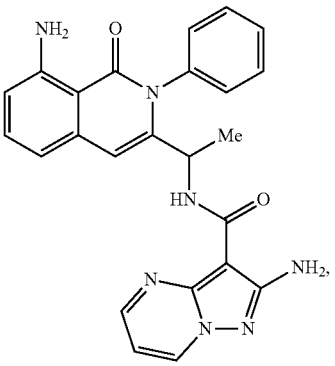


TABLE 8

Compound 1001'

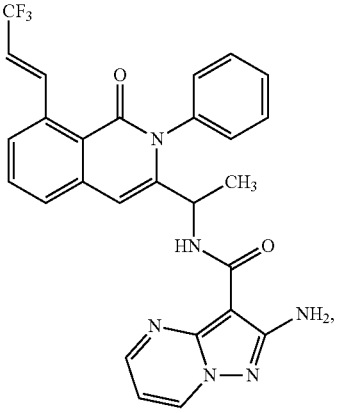
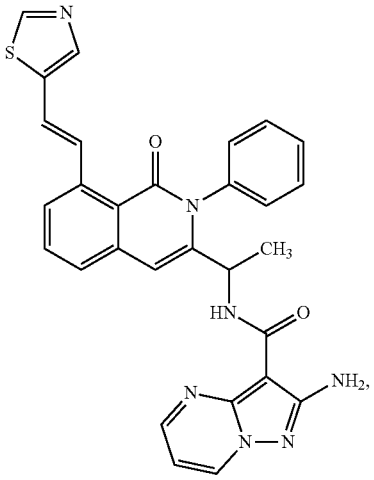
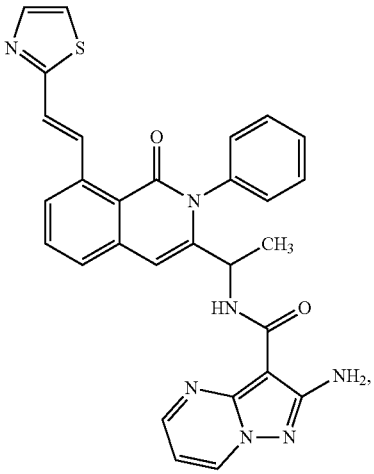


TABLE 8-continued

Compound 1002'



Compound 1003'



Compound 1004'

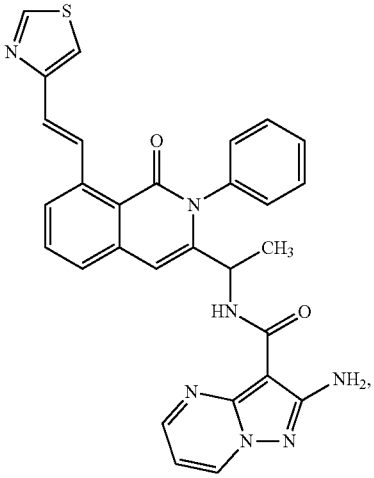
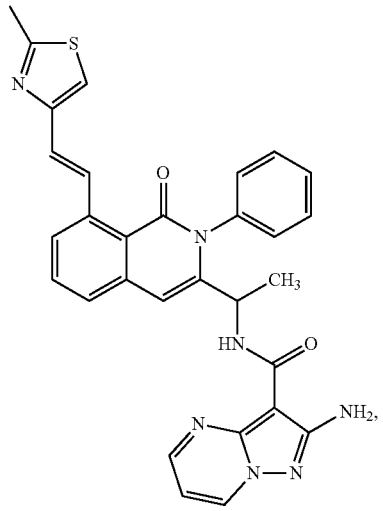
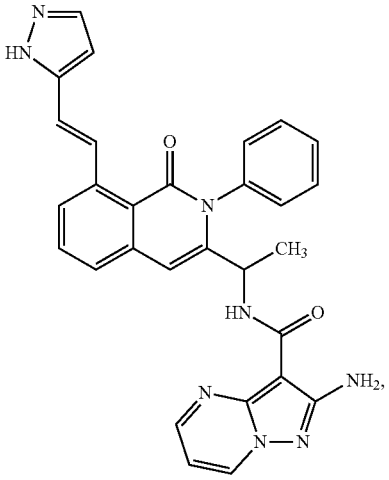


TABLE 8-continued

Compound 1005'



Compound 1006'



Compound 1007'

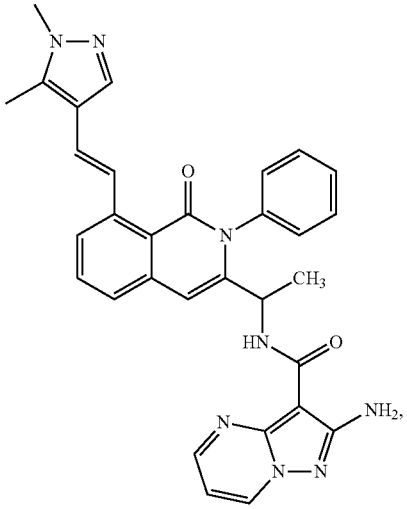
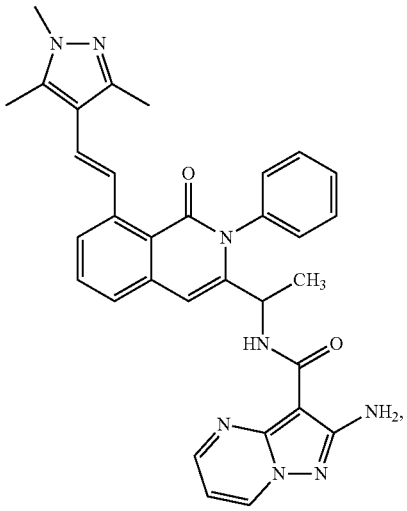
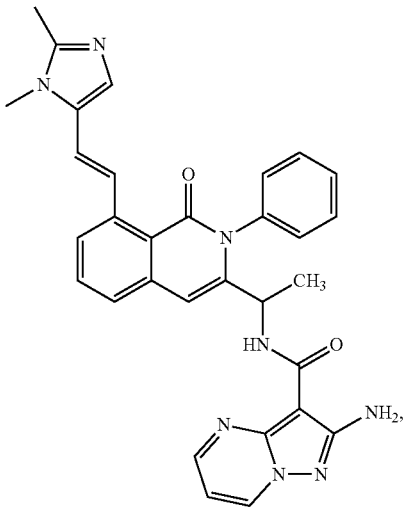


TABLE 8-continued

Compound 1008'



Compound 1009'



Compound 1010'

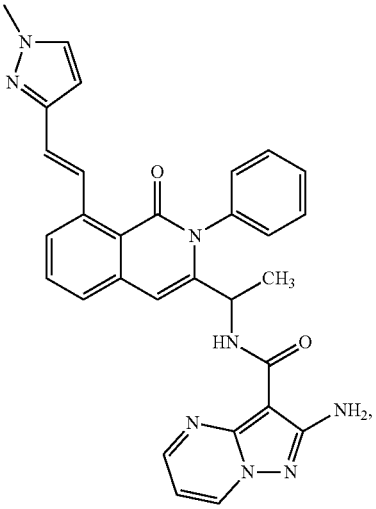


TABLE 8-continued

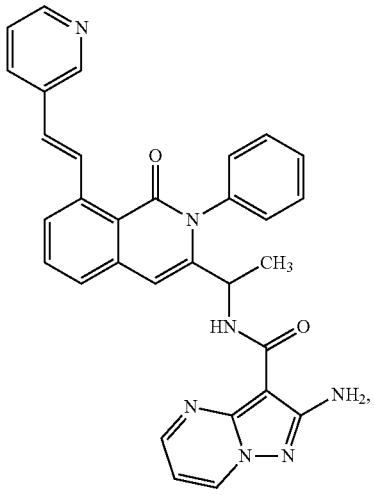
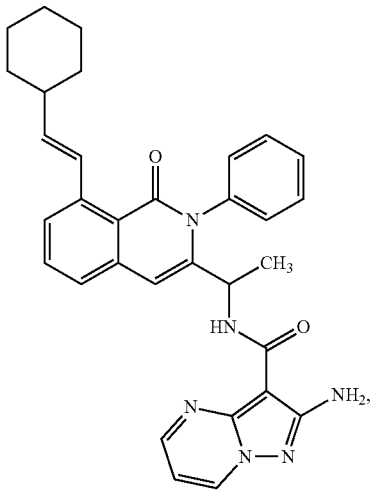
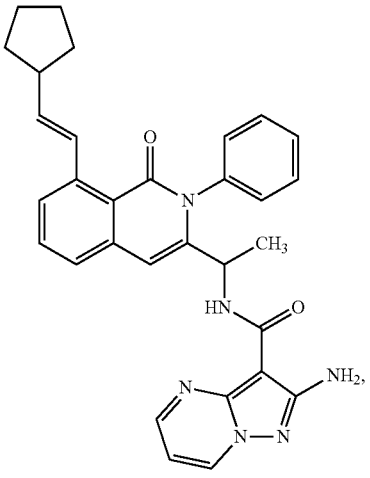
Compound 1011'	
Compound 1012'	
Compound 1013'	

TABLE 8-continued

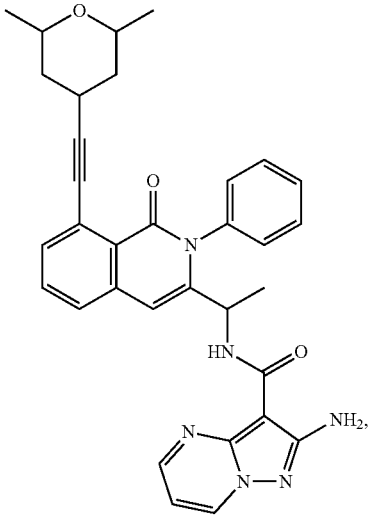
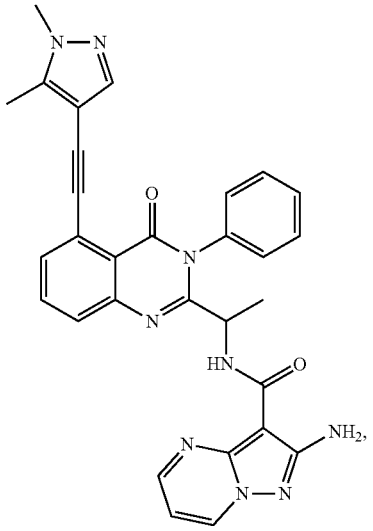
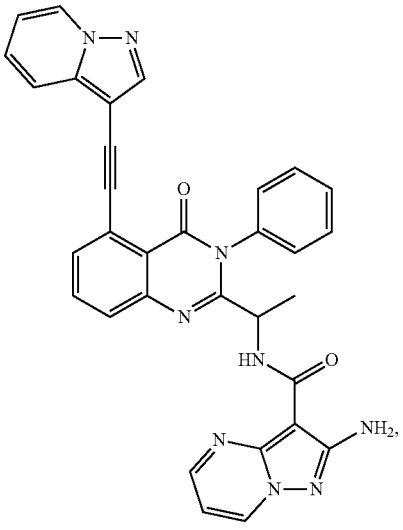
Compound 1014'	
Compound 1015'	
Compound 1016'	

TABLE 8-continued

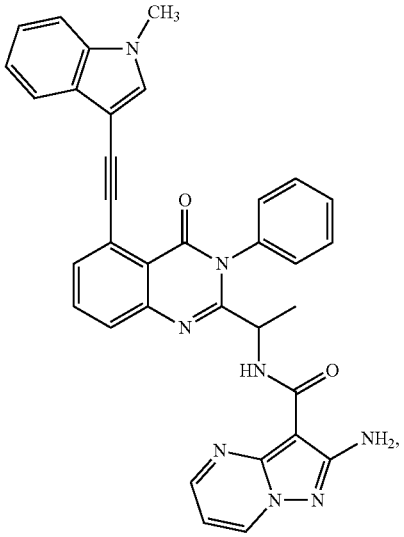
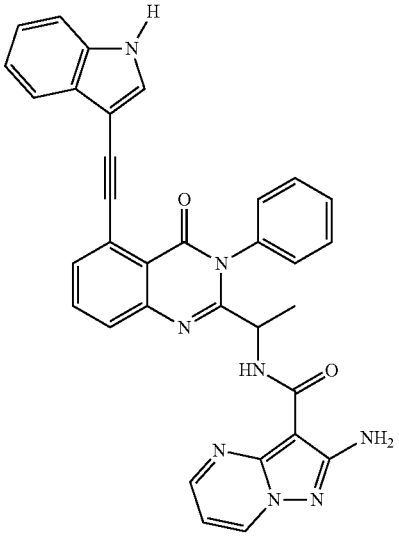
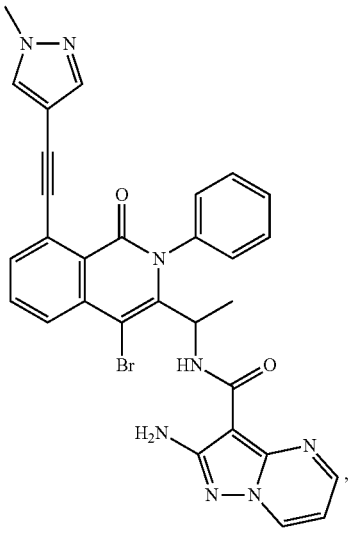
Compound 1017'	
Compound 1018'	
Compound 1041'	

TABLE 8-continued

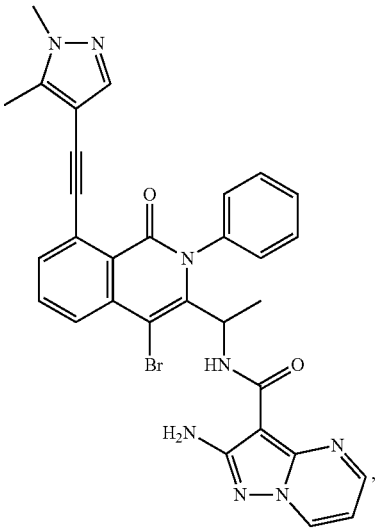
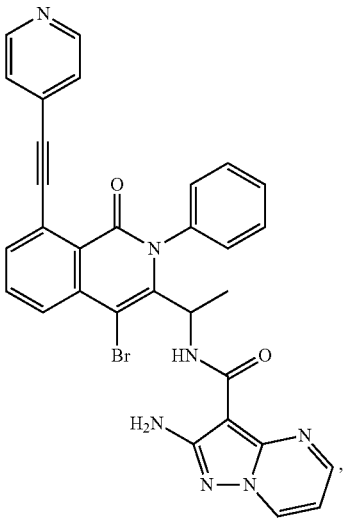
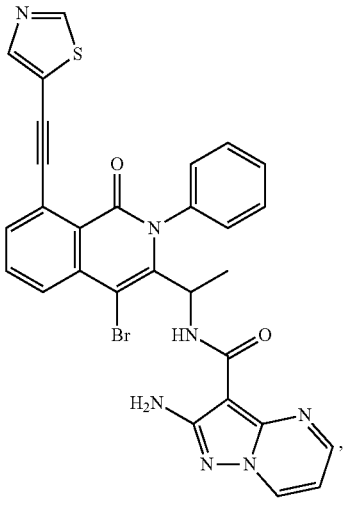
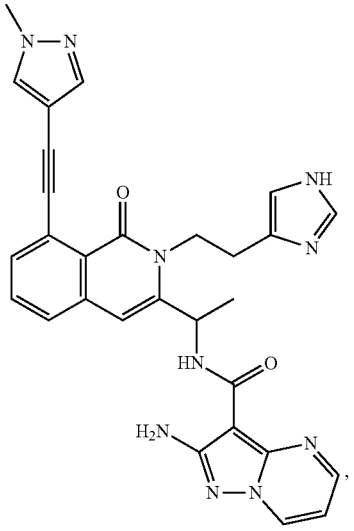
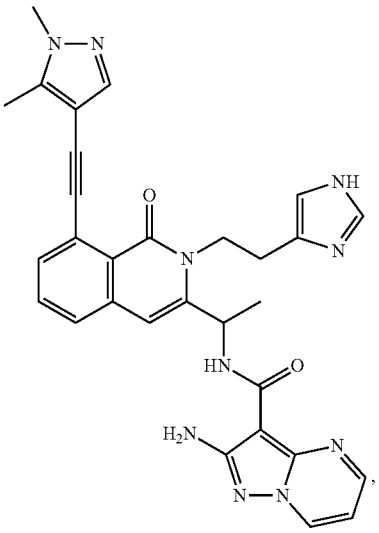
Compound 1042'	
Compound 1043'	
Compound 1044'	

TABLE 8-continued

Compound 1045'



Compound 1046'



Compound 1047'

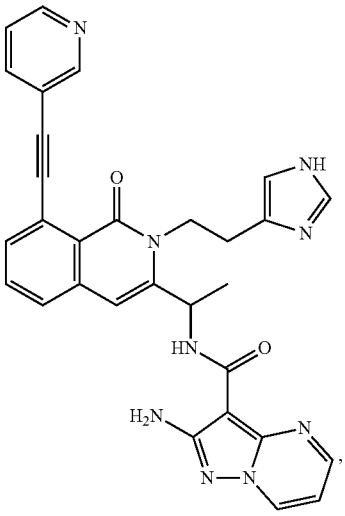
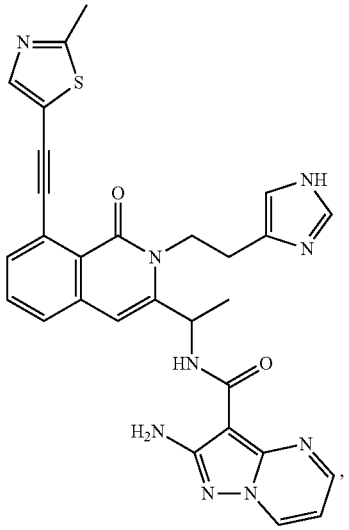
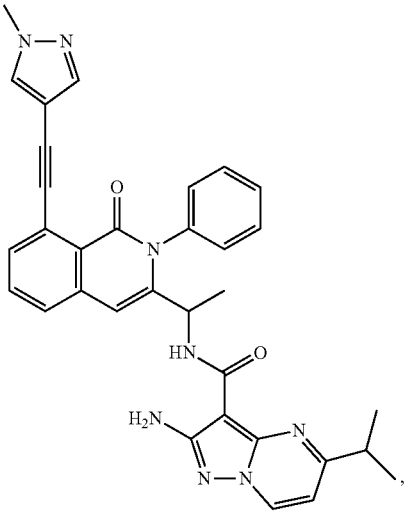


TABLE 8-continued

Compound 1048'



Compound 1049'



Compound 1050'

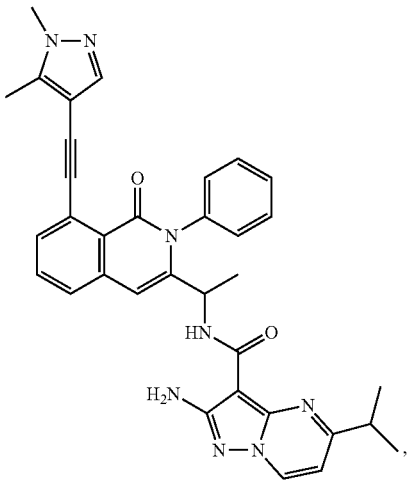


TABLE 8-continued

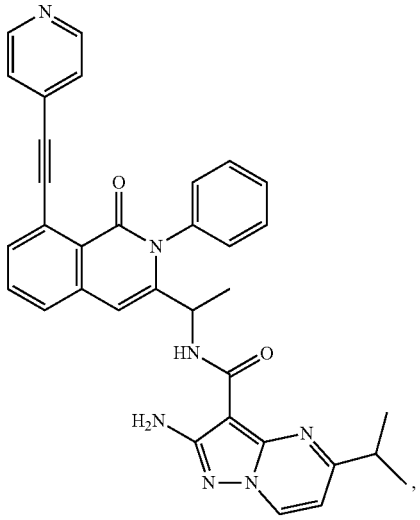
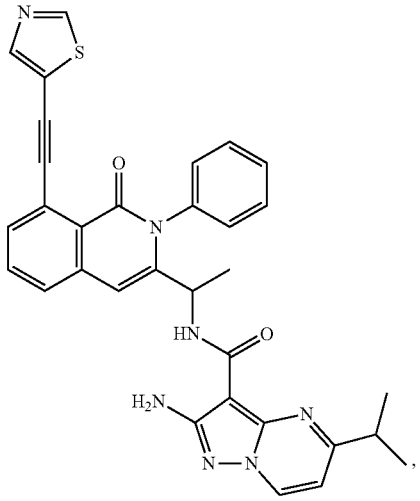
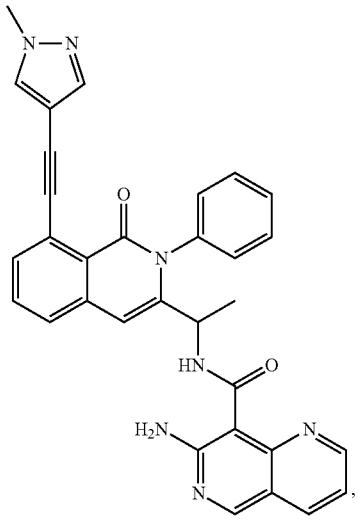
Compound 1051'	
Compound 1052'	
Compound 1053'	

TABLE 8-continued

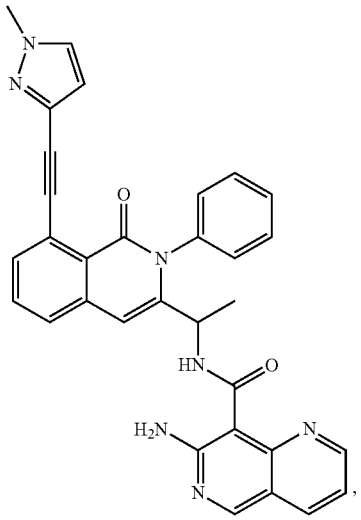
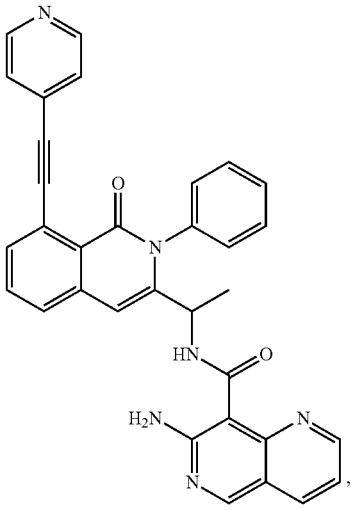
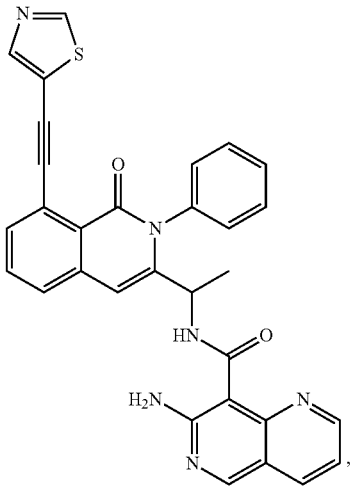
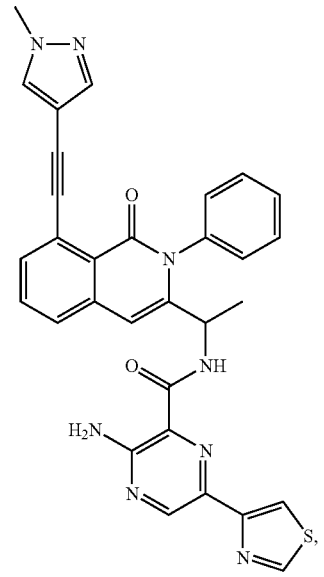
Compound 1054'	
Compound 1055'	
Compound 1056'	

TABLE 8-continued

Compound 1057'



Compound 1058'

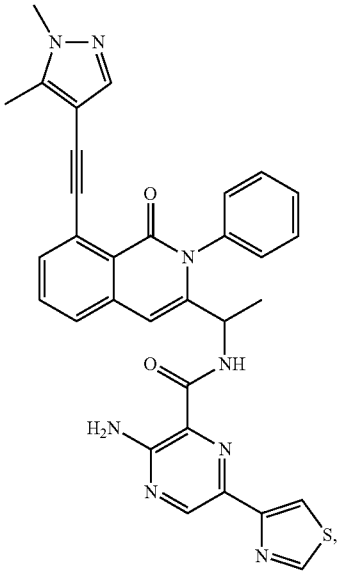
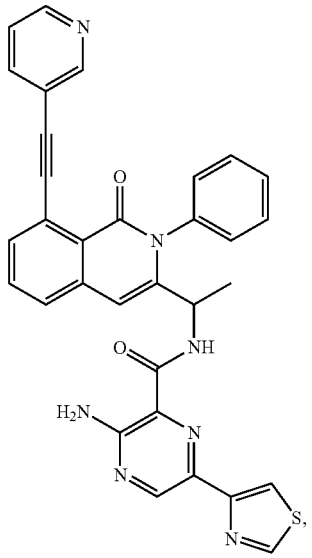
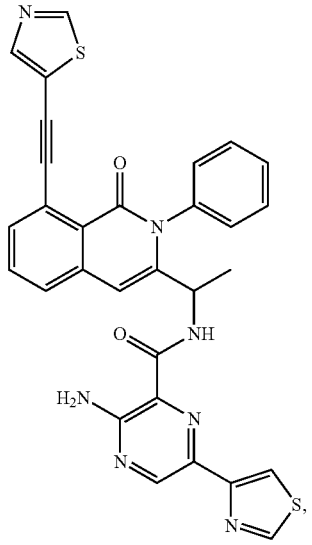


TABLE 8-continued

Compound 1059'



Compound 1060'



Compound 1061'

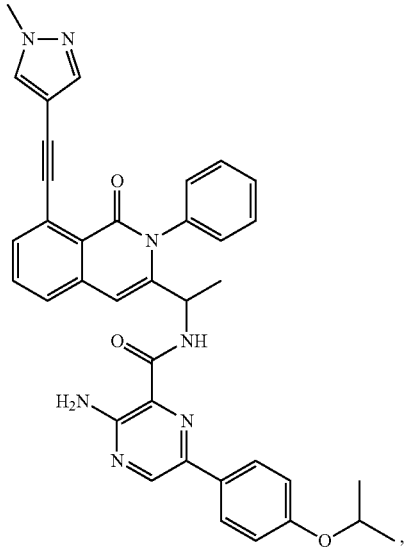
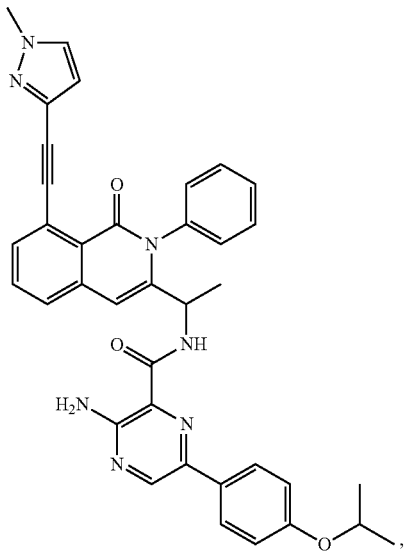


TABLE 8-continued

Compound 1062'



Compound 1063'

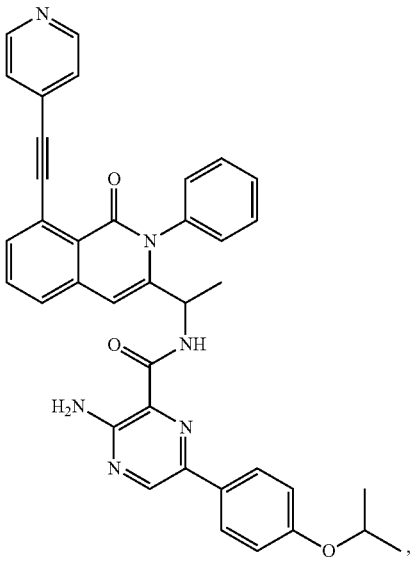
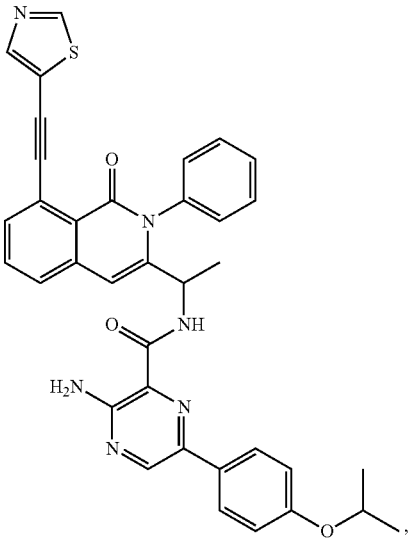


TABLE 8-continued

Compound 1064'



Compound 1065'

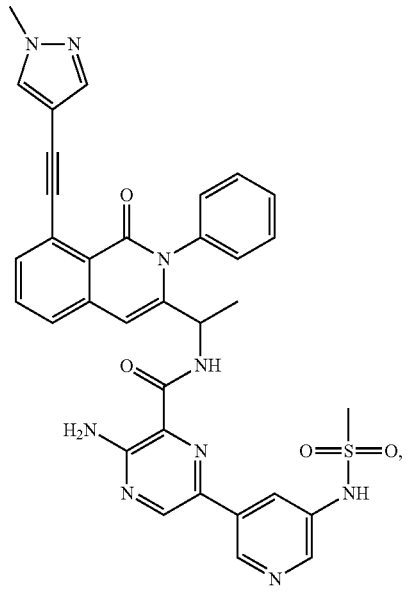
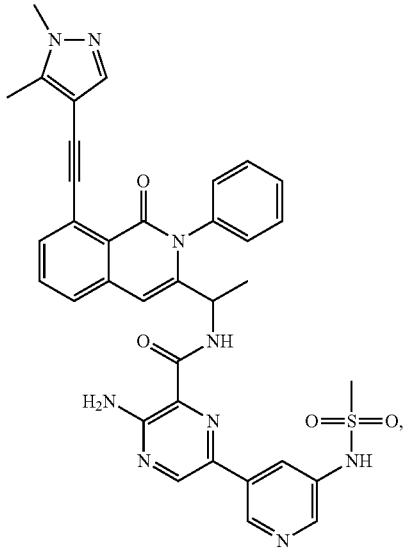


TABLE 8-continued

Compound 1066'



Compound 1067'

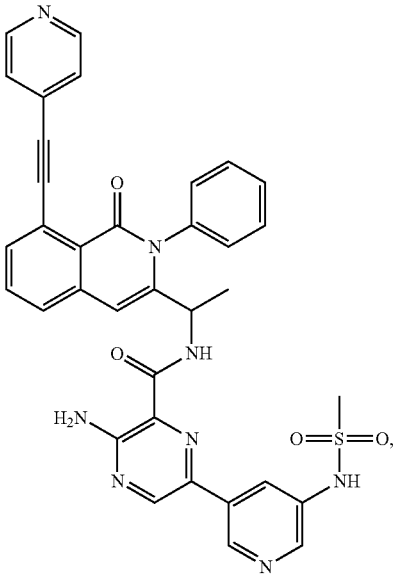
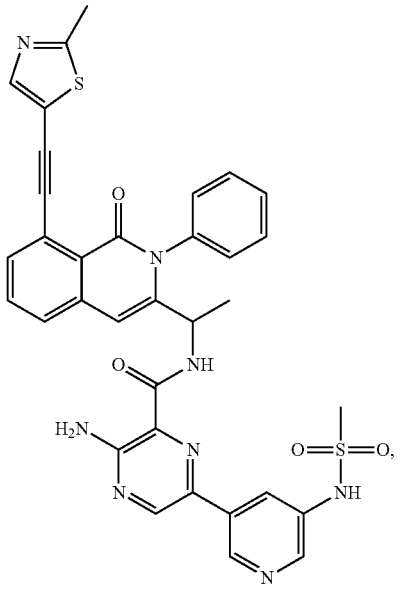
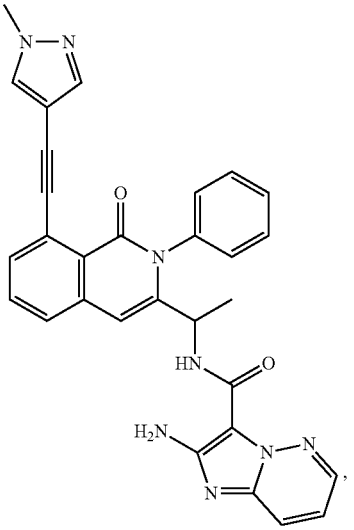


TABLE 8-continued

Compound 1068'



Compound 1069'



Compound 1070'

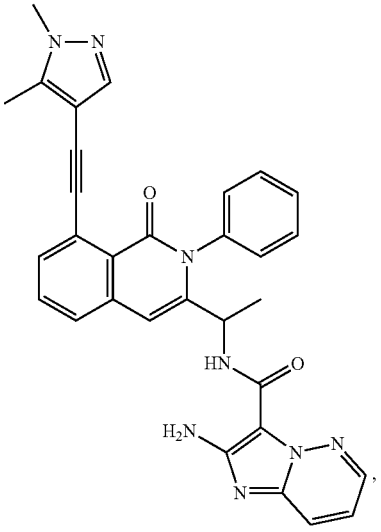


TABLE 8-continued

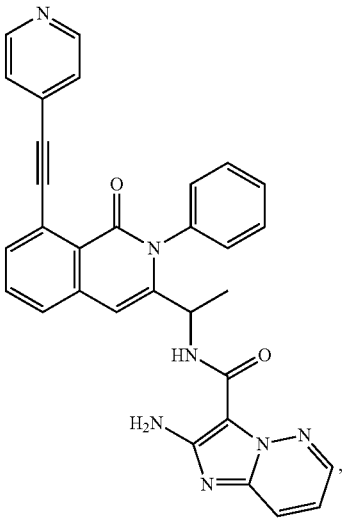
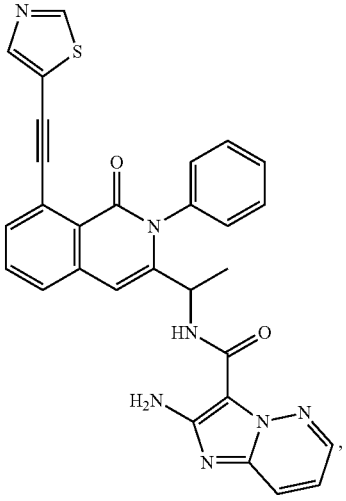
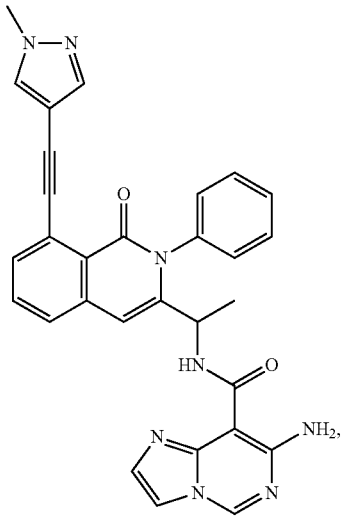
Compound 1071'	
Compound 1072'	
Compound 1073'	

TABLE 8-continued

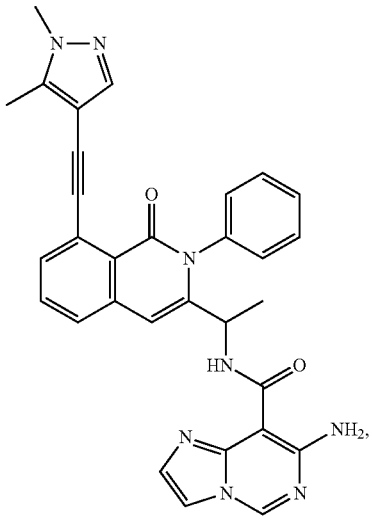
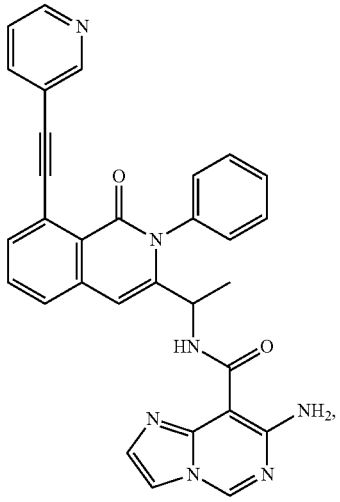
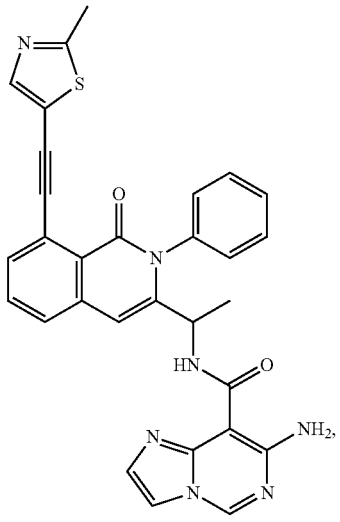
Compound 1074'	
Compound 1075'	
Compound 1076'	

TABLE 8-continued

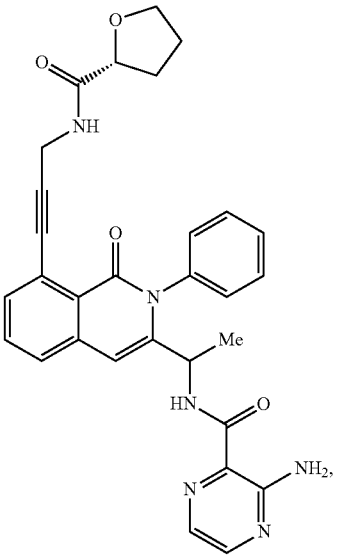
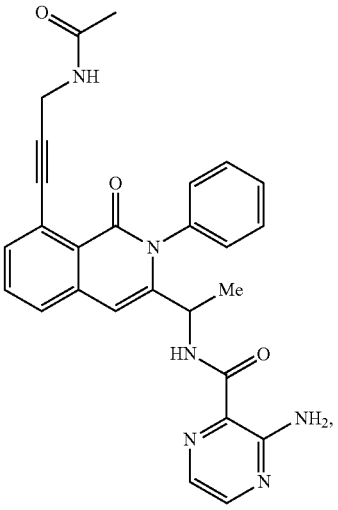
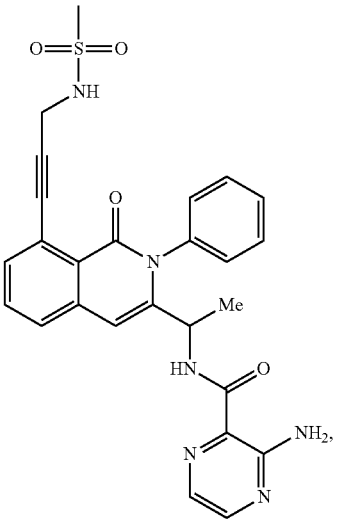
Compound 1077'	
Compound 1078'	
Compound 1079'	

TABLE 8-continued

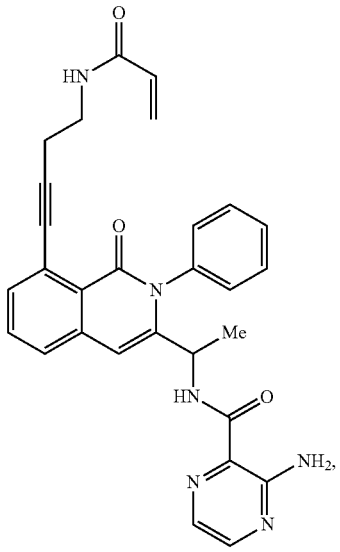
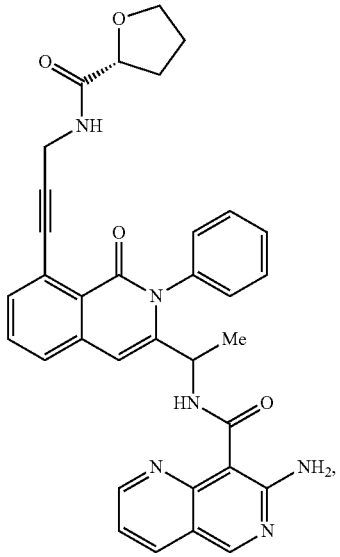
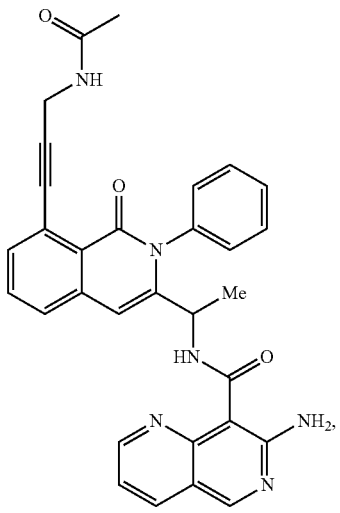
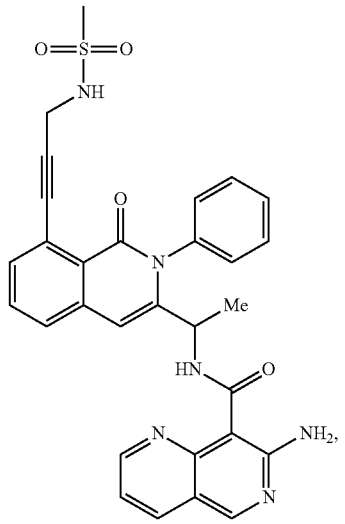
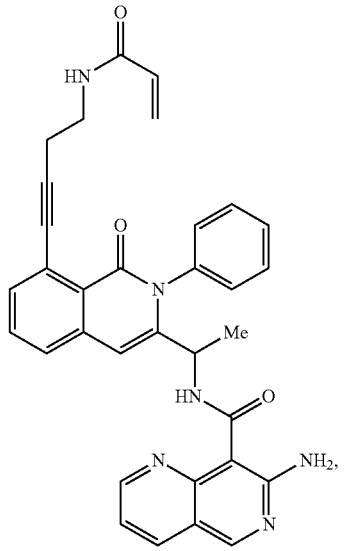
Compound 1080'	
Compound 1081'	
Compound 1082'	

TABLE 8-continued

Compound 1083'



Compound 1084'



Compound 1085'

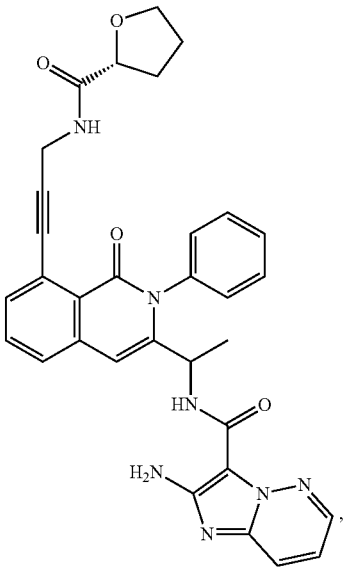
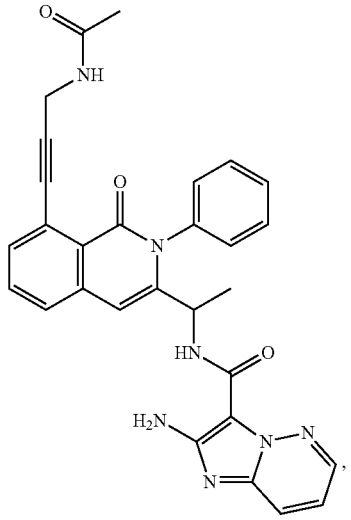
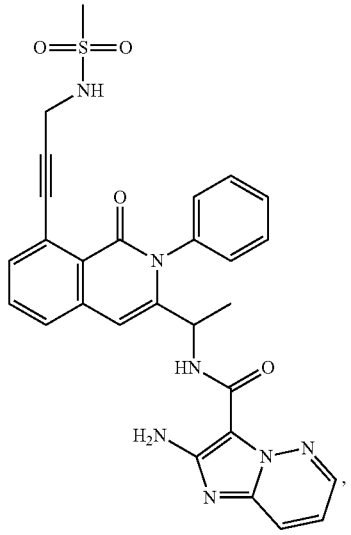


TABLE 8-continued

Compound 1086'



Compound 1087'



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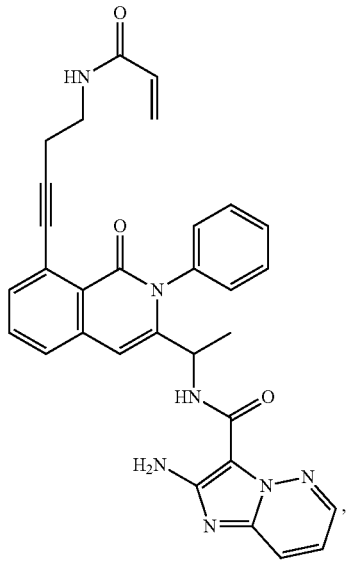
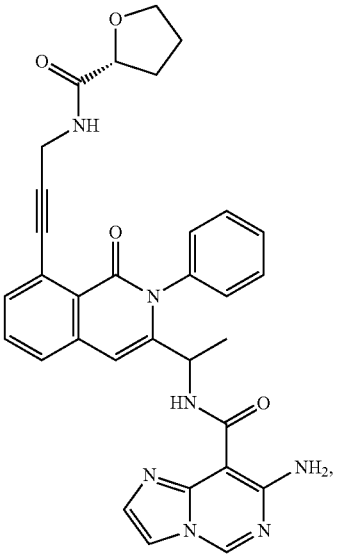


TABLE 8-continued

Compound 1089'



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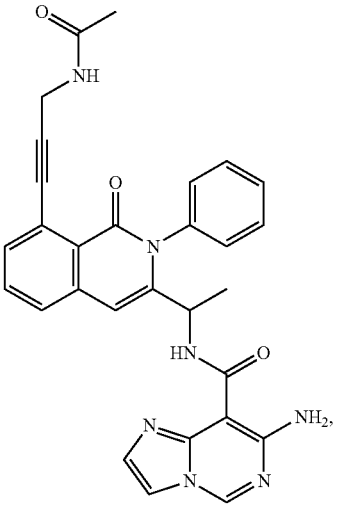


Compound 1091'

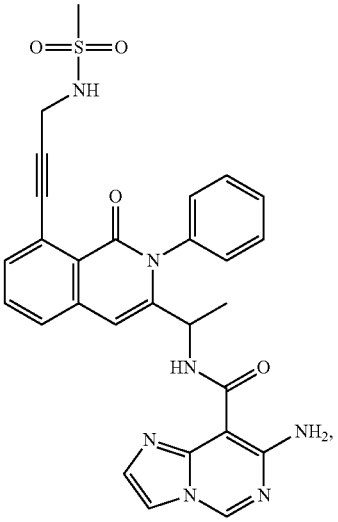


TABLE 8-continued

Compound 1092'

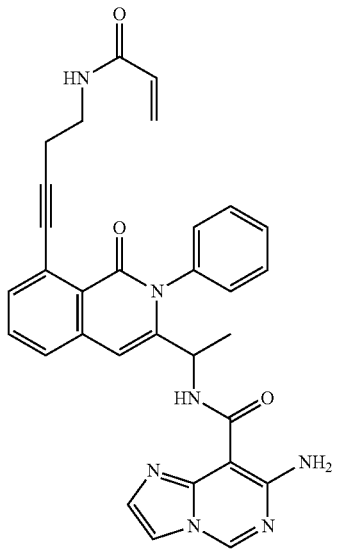
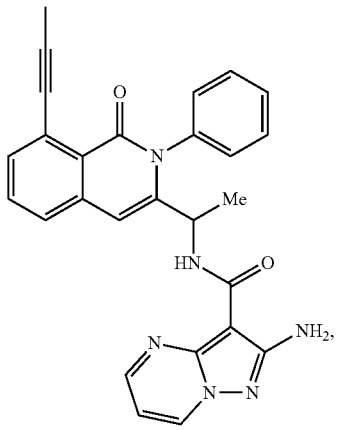


TABLE 9

Compound 2001'



Compound 2002'

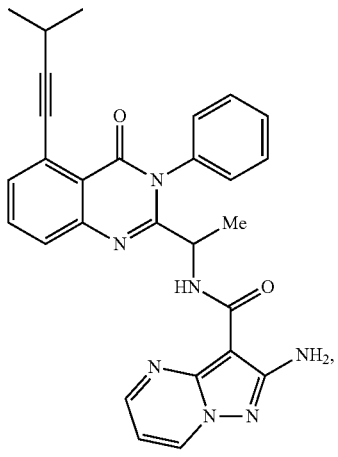


TABLE 9-continued

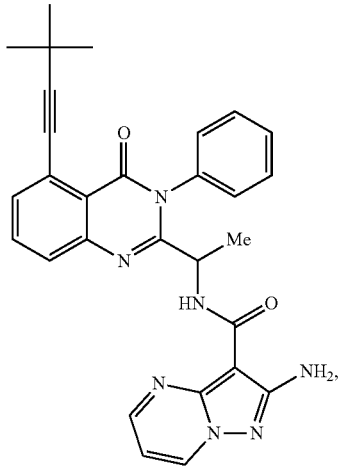
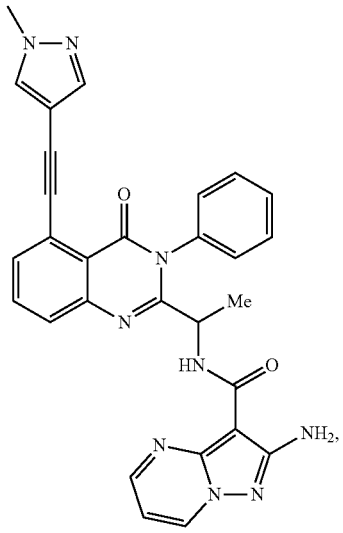
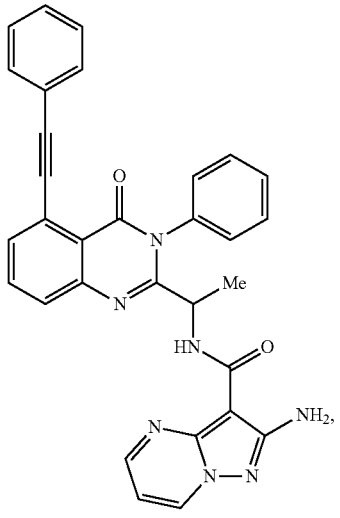
Compound 2003'	
Compound 2004'	
Compound 2005'	

TABLE 9-continued

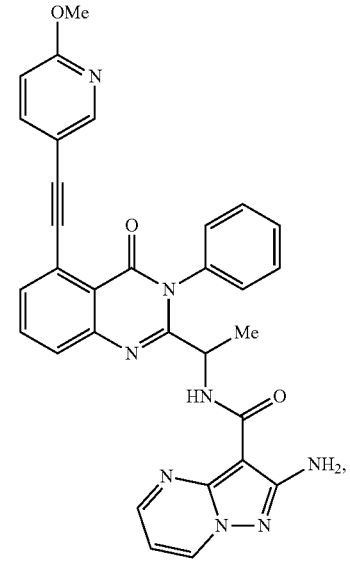
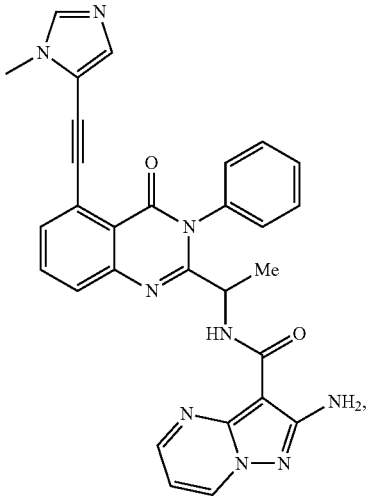
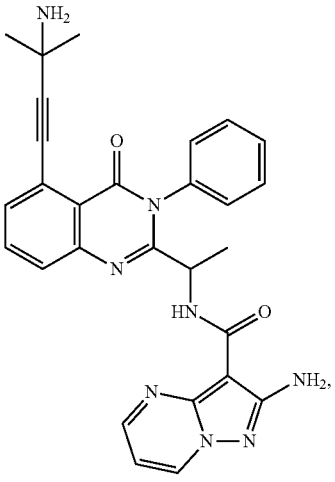
Compound 2006'	
Compound 2007'	
Compound 2008'	

TABLE 9-continued

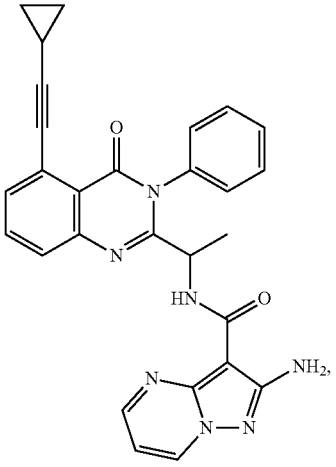
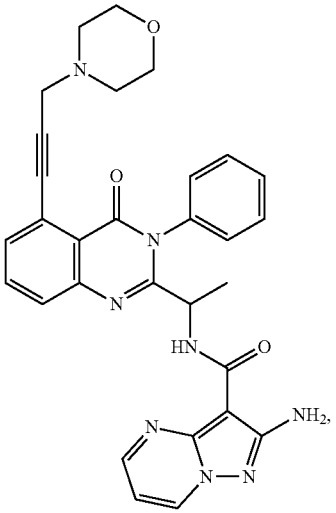
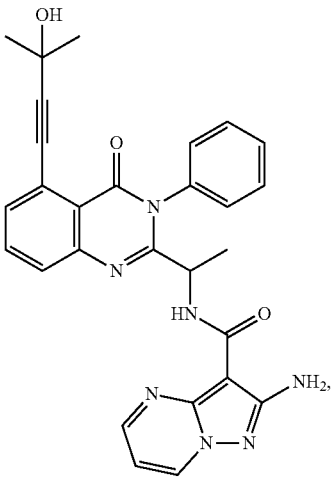
Compound 2009'	
Compound 2010'	
Compound 2011'	

TABLE 9-continued

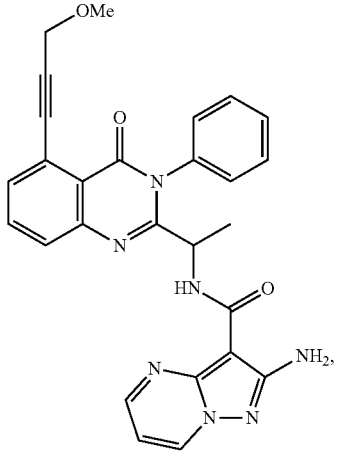
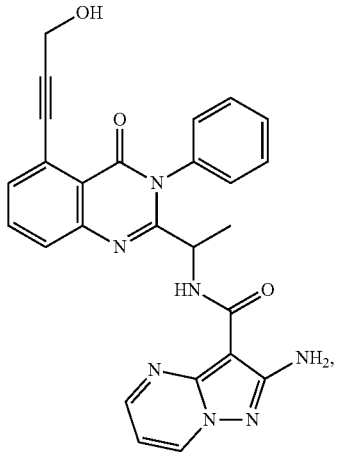
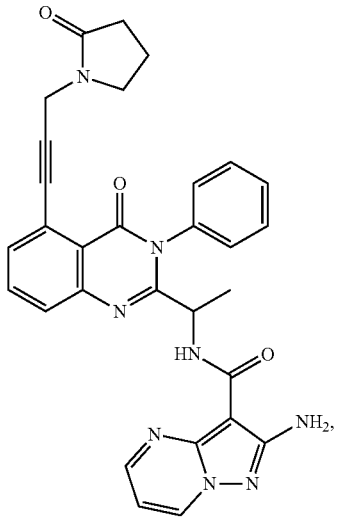
Compound 2012'	
Compound 2013'	
Compound 2014'	

TABLE 9-continued

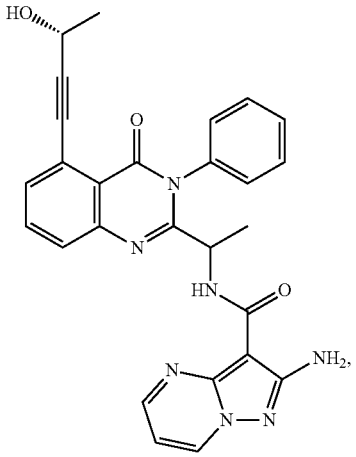
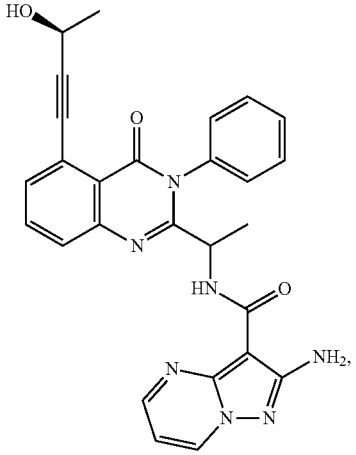
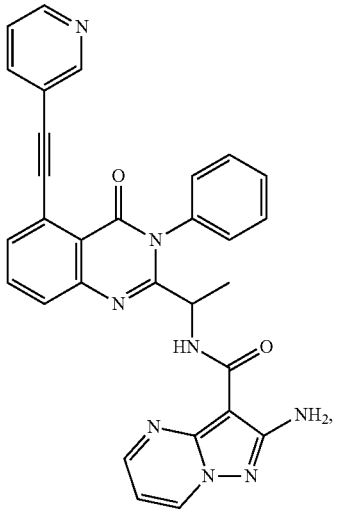
Compound 2015'	
Compound 2016'	
Compound 2017'	

TABLE 9-continued

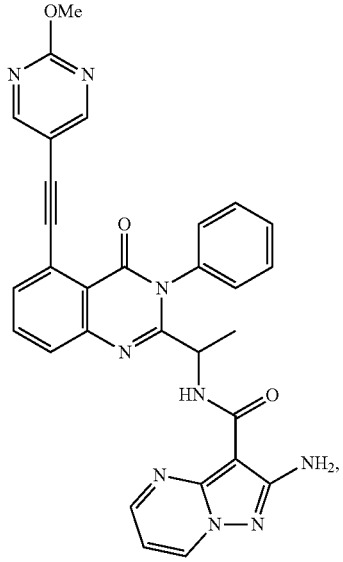
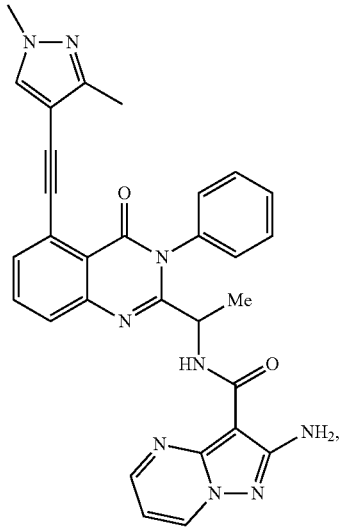
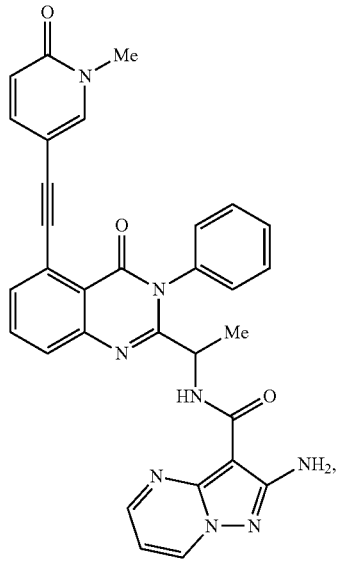
Compound 2018'	
Compound 2019'	
Compound 2020'	

TABLE 9-continued

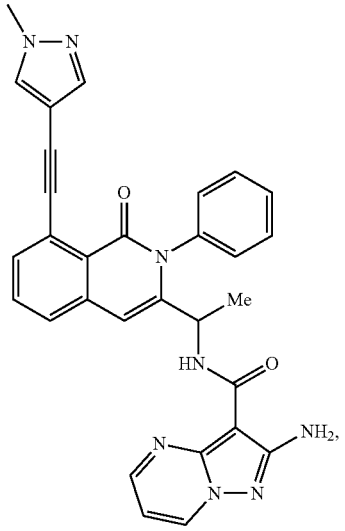
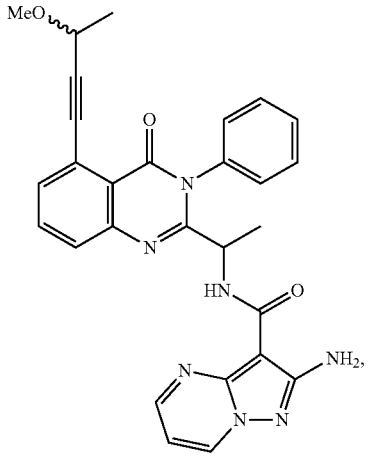
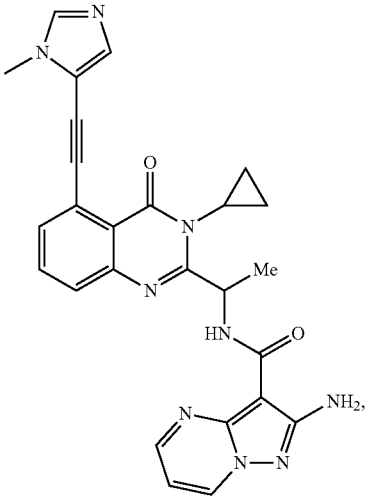
Compound 2021'	
Compound 2022'	
Compound 2023'	

TABLE 9-continued

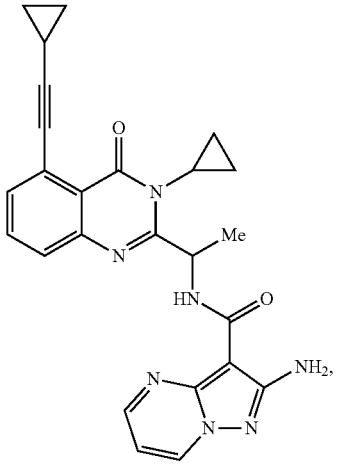
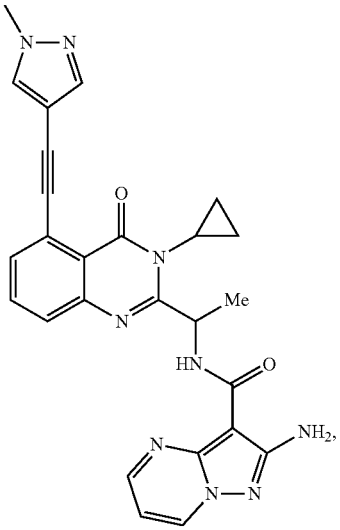
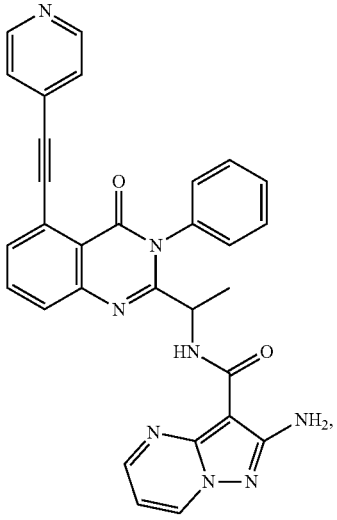
Compound 2024'	
Compound 2025'	
Compound 2026'	

TABLE 9-continued

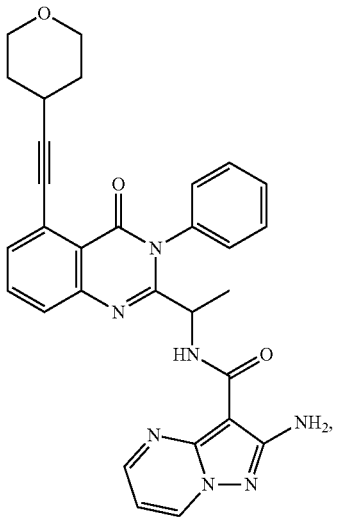
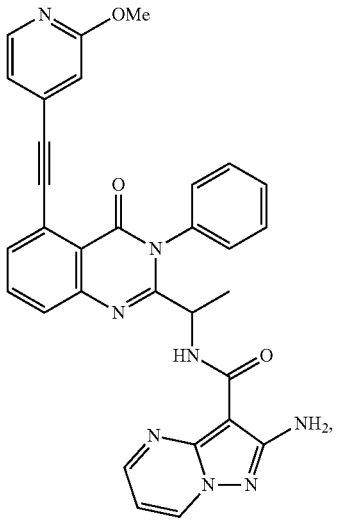
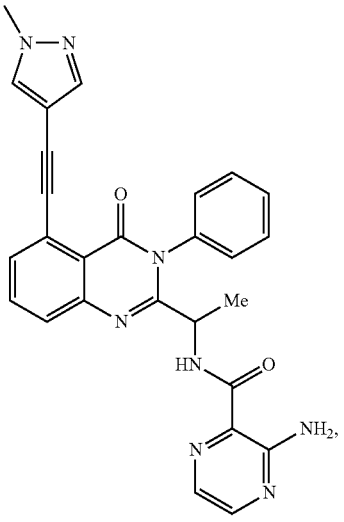
Compound 2027'	
Compound 2028'	
Compound 2029'	

TABLE 9-continued

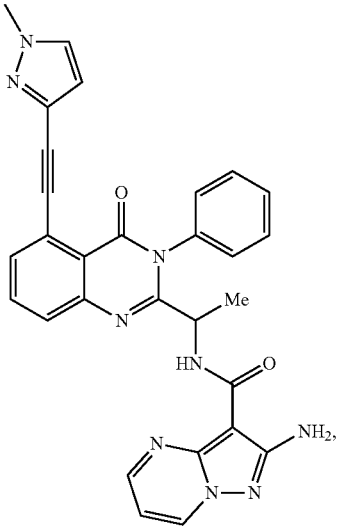
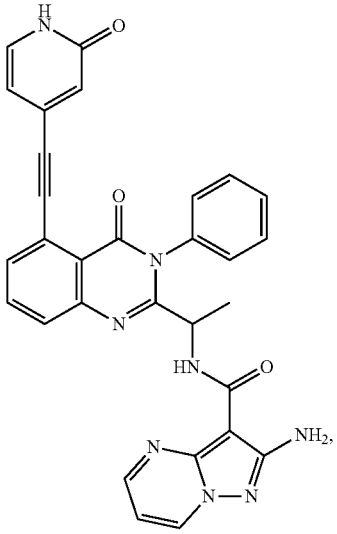
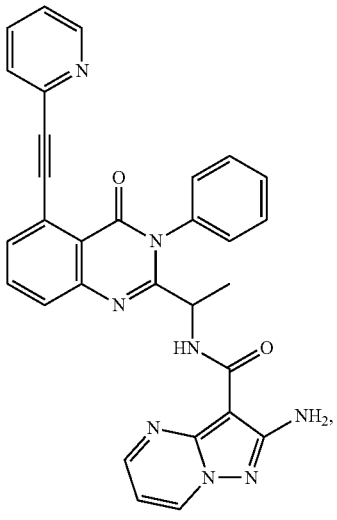
Compound 2030'	
Compound 2031'	
Compound 2032'	

TABLE 9-continued

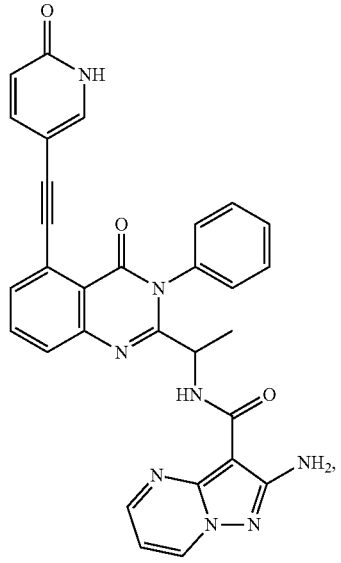
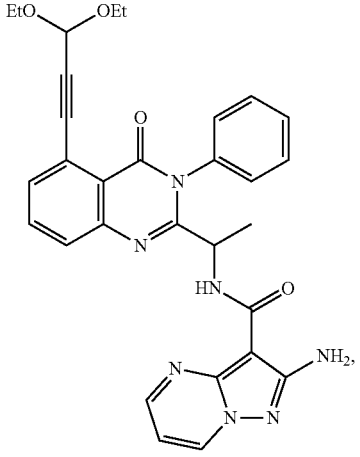
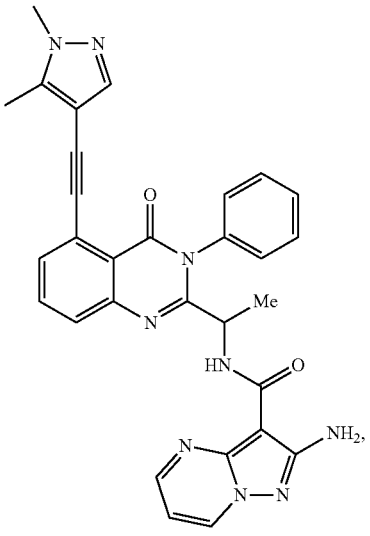
Compound 2033'	
Compound 2034'	
Compound 2035'	

TABLE 9-continued

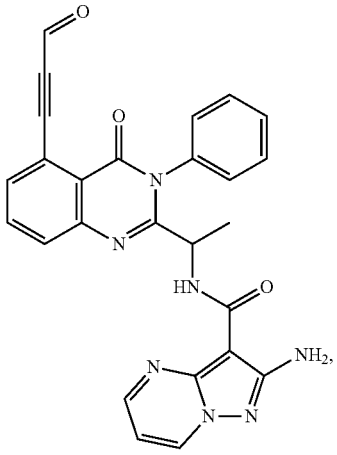
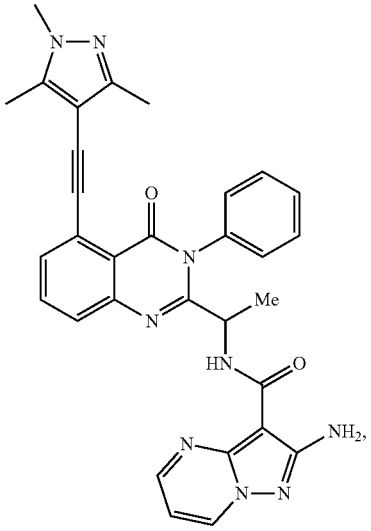
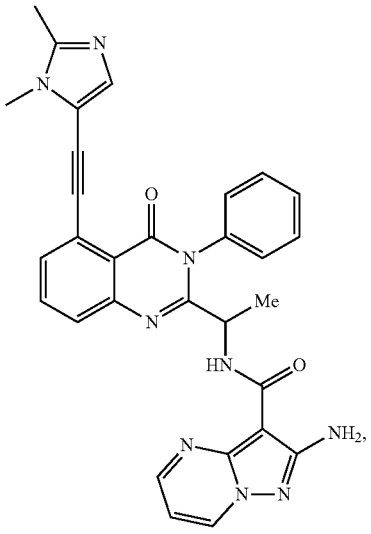
Compound 2036'	
Compound 2037'	
Compound 2038'	

TABLE 9-continued

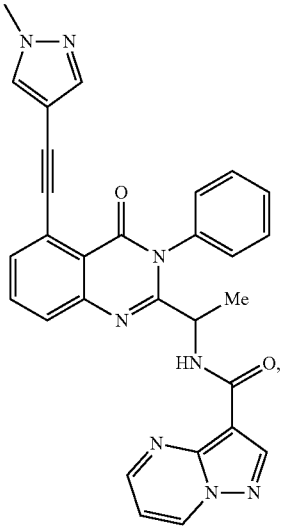
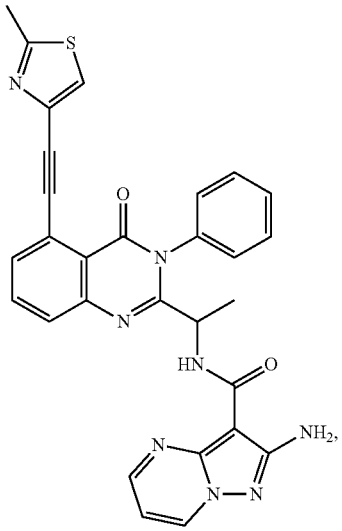
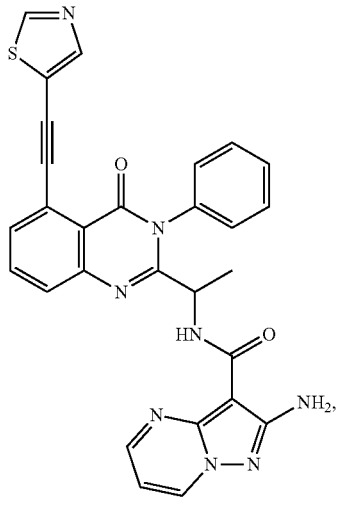
Compound 2039'	
Compound 2040'	
Compound 2041'	

TABLE 9-continued

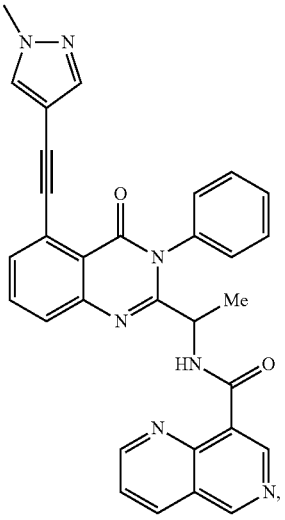
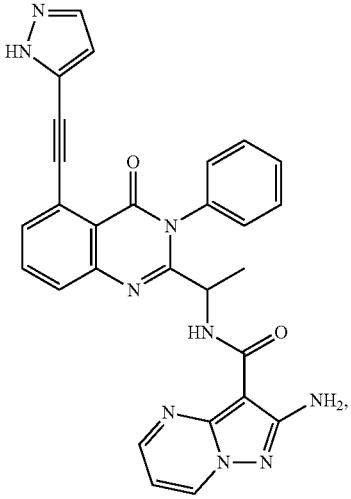
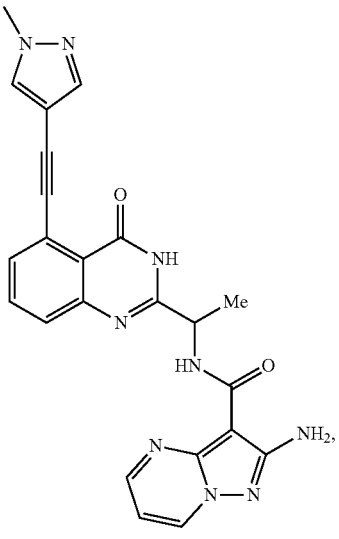
Compound 2042'	
Compound 2043'	
Compound 2044'	

TABLE 9-continued

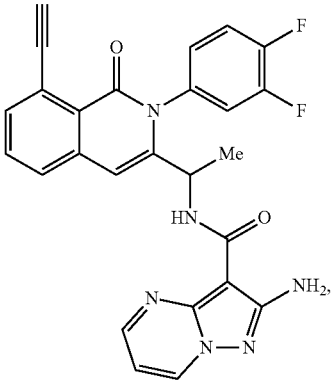
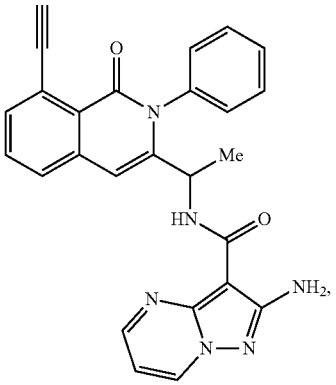
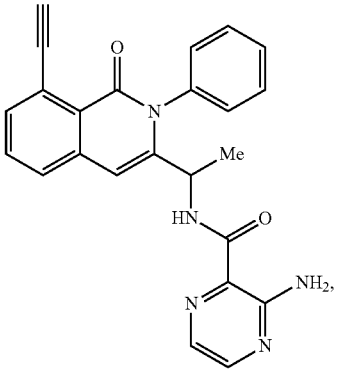
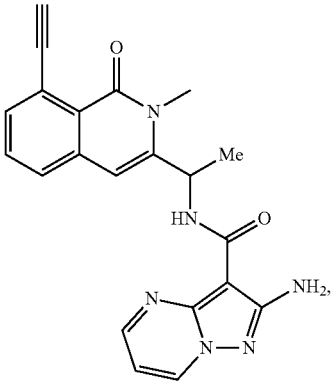
Compound 2045'	
Compound 2046'	
Compound 2047'	
Compound 2048'	

TABLE 9-continued

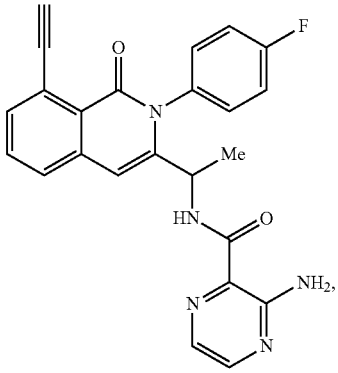
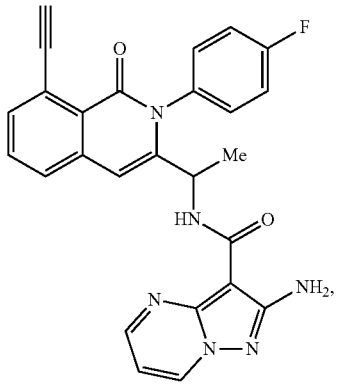
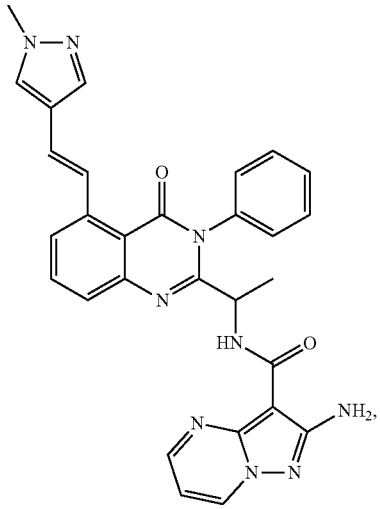
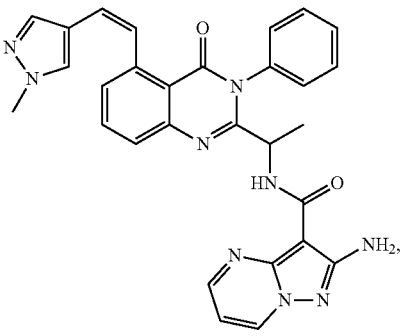
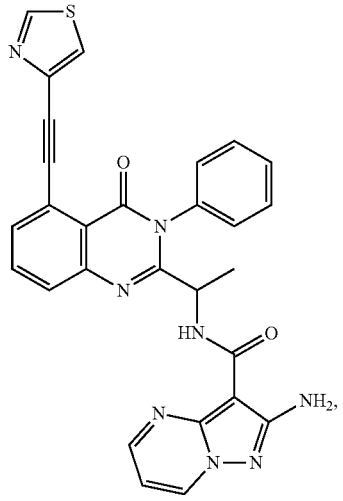
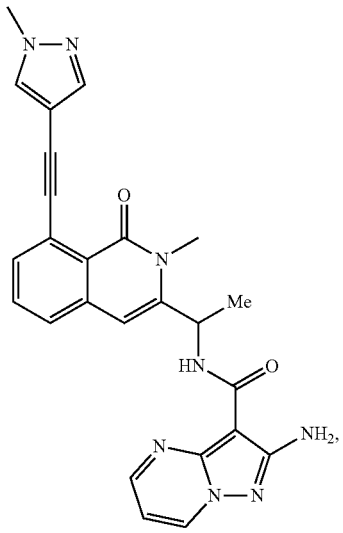
Compound 2049'	
Compound 2050'	
Compound 2052'	
Compound 2053'	

TABLE 9-continued

Compound 2054'



Compound 2055'



Compound 2056'

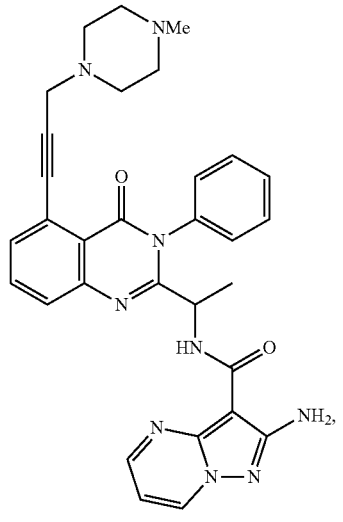
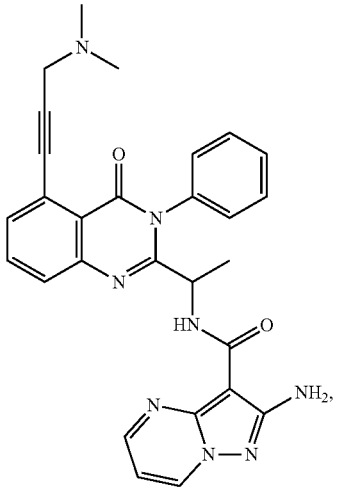
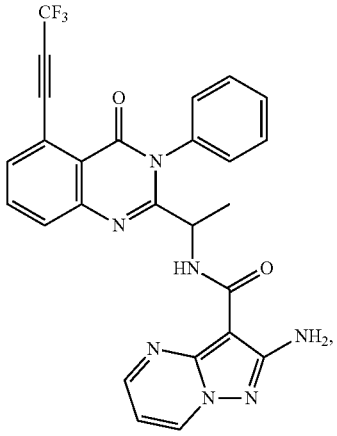


TABLE 9-continued

Compound 2057'



Compound 2058'



Compound 2059'

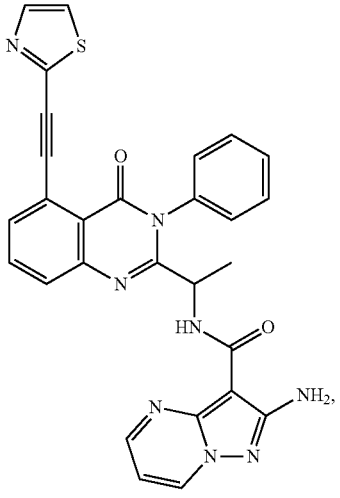


TABLE 9-continued

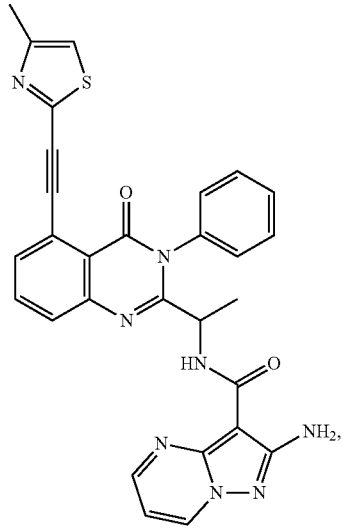
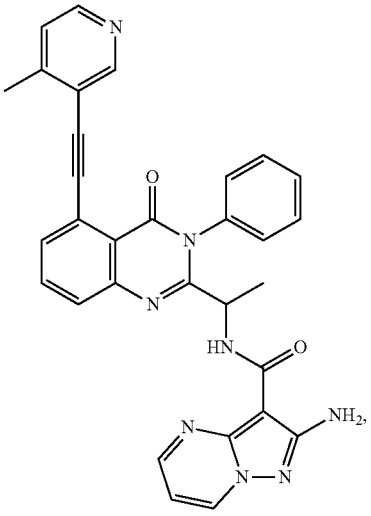
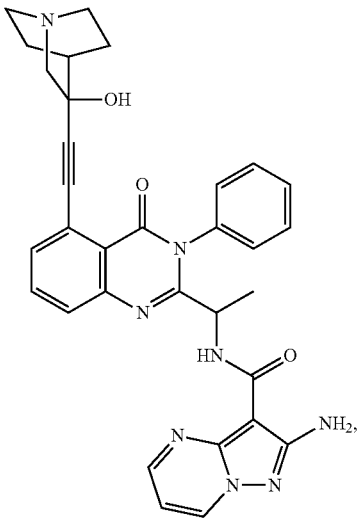
Compound 2060'	
Compound 2061'	
Compound 2062'	

TABLE 9-continued

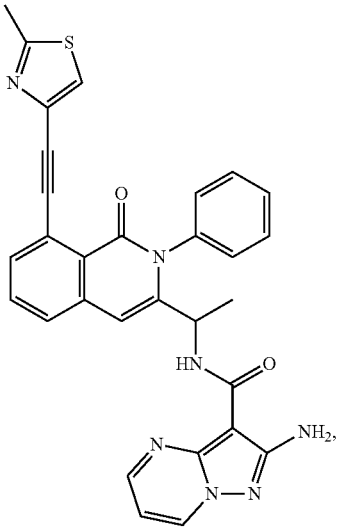
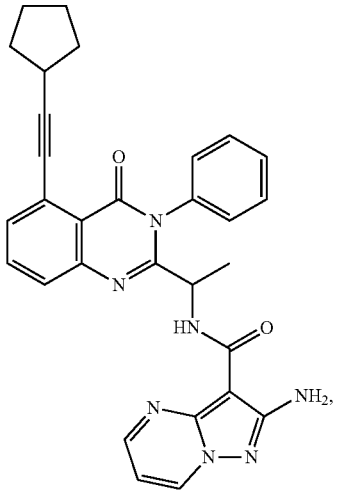
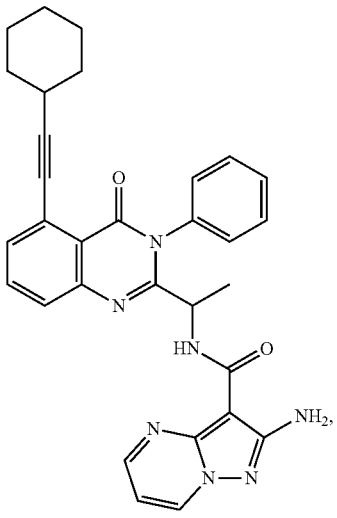
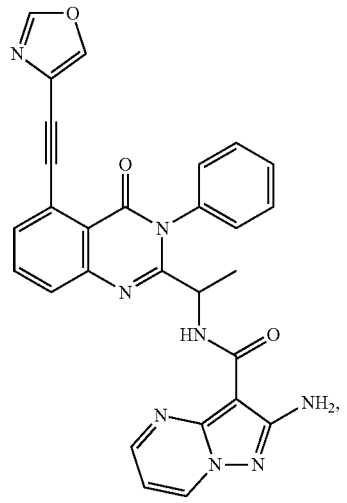
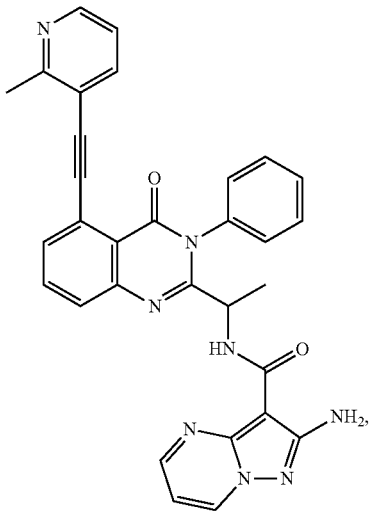
Compound 2063'	
Compound 2064'	
Compound 2065'	

TABLE 9-continued

Compound 2066'



Compound 2067'



Compound 2068'

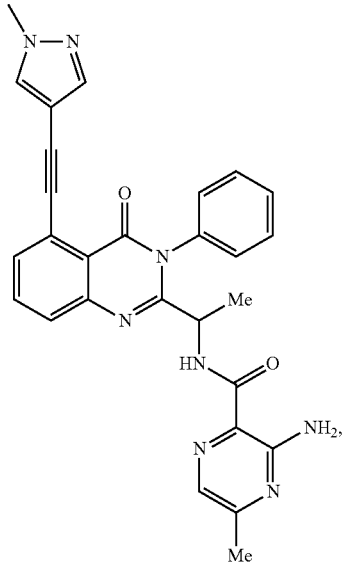
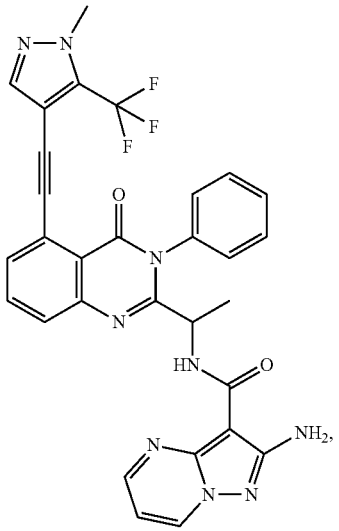
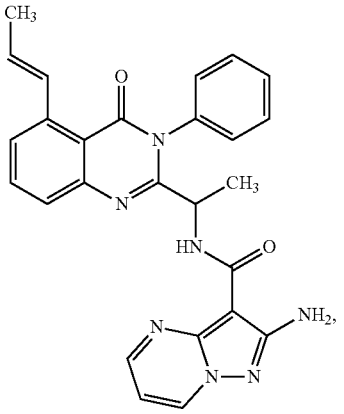


TABLE 9-continued

Compound 2069'



Compound 2070'



Compound 2071'

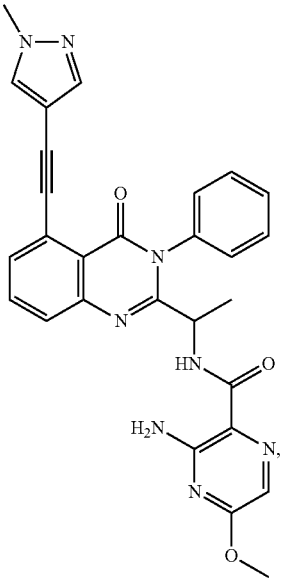


TABLE 9-continued

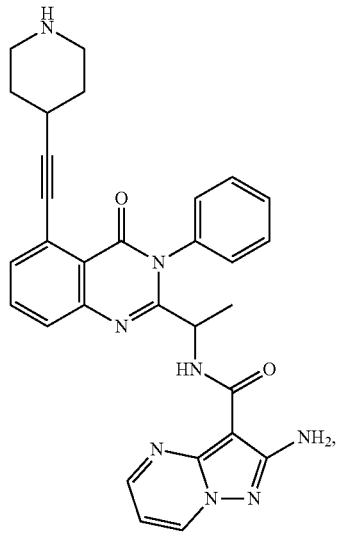
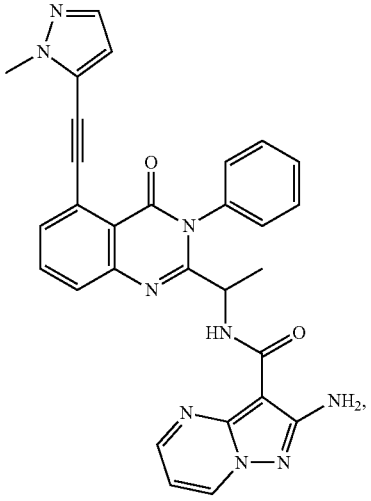
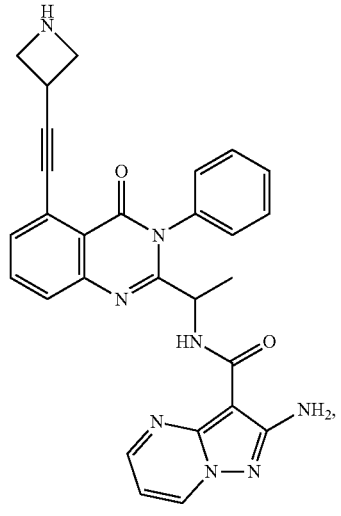
Compound 2072'	
Compound 2073'	
Compound 2074'	

TABLE 9-continued

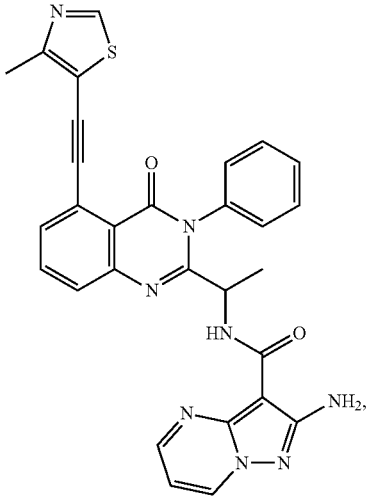
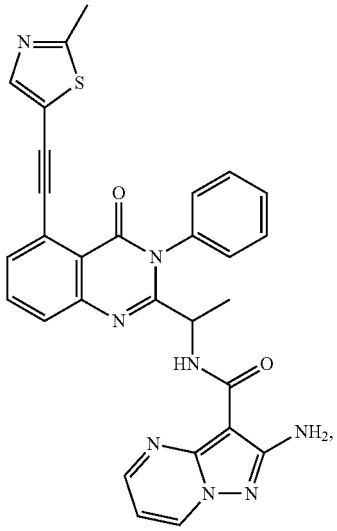
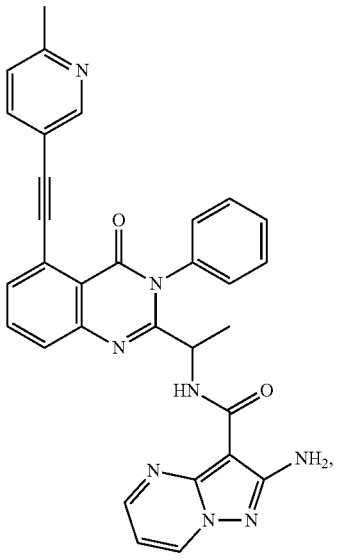
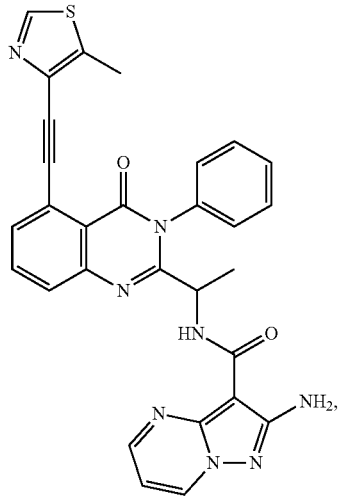
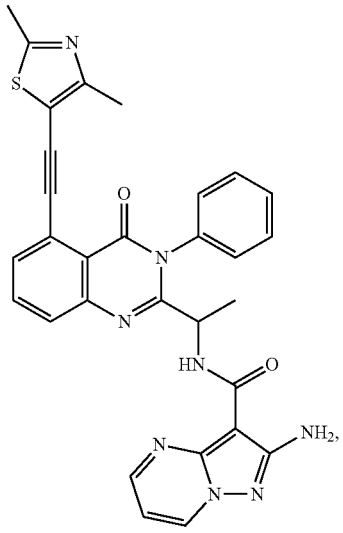
Compound 2075'	
Compound 2076'	
Compound 2077'	

TABLE 9-continued

Compound 2078'



Compound 2079'



Compound 2080'

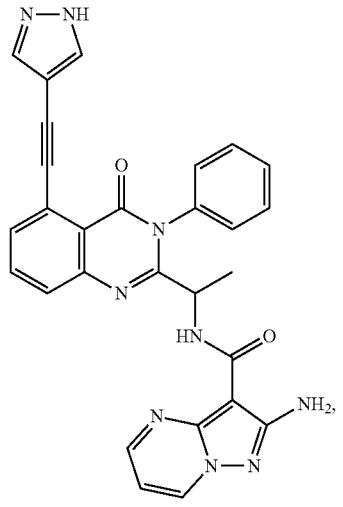
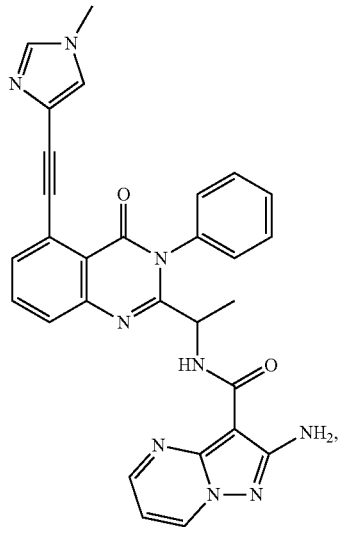


TABLE 9-continued

Compound 2081'



Compound 2082'

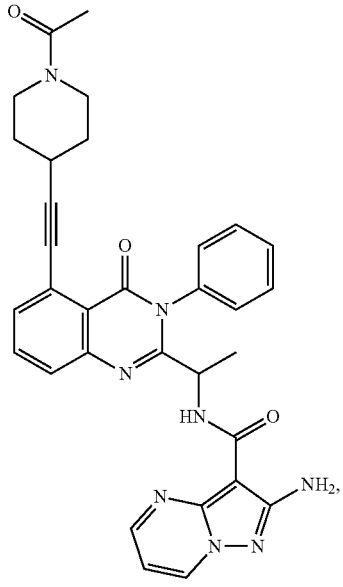
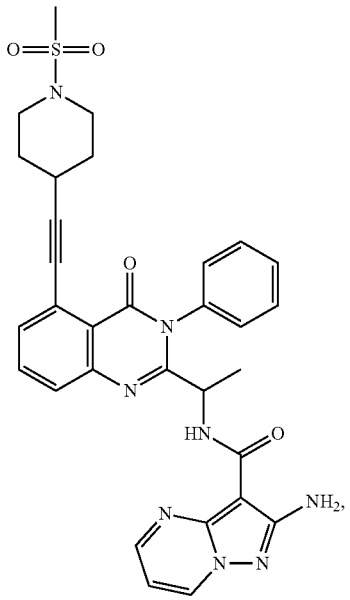
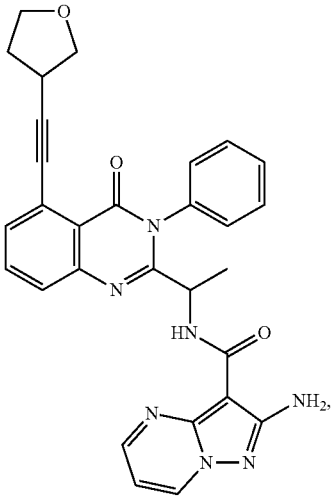


TABLE 9-continued

Compound 2083'



Compound 2084'



Compound 2085'

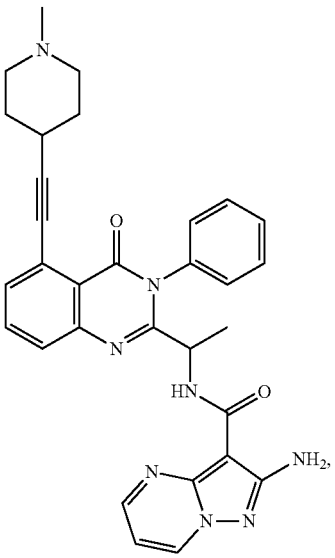
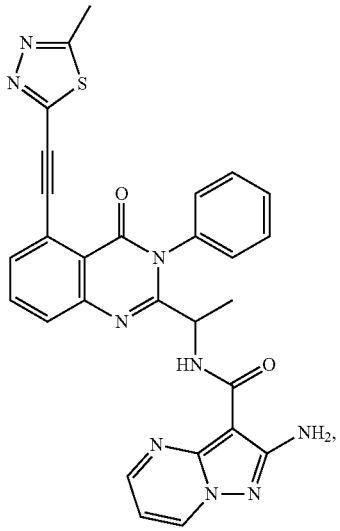
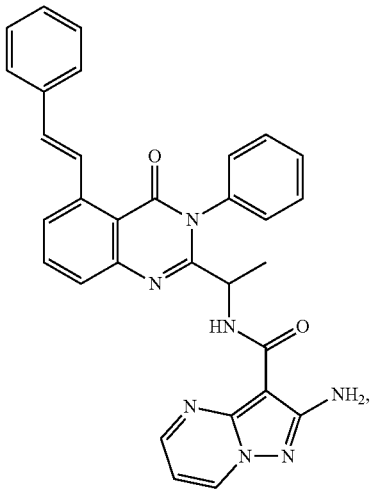


TABLE 9-continued

Compound 2086'



Compound 2087'



Compound 2088'

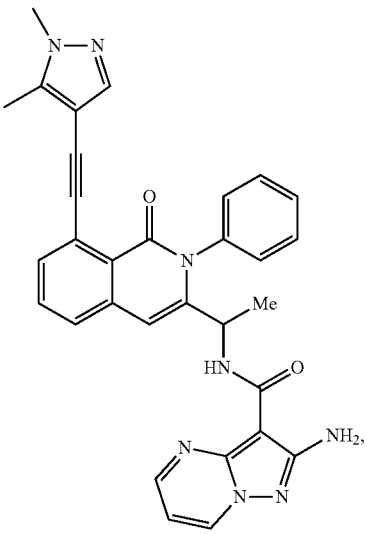
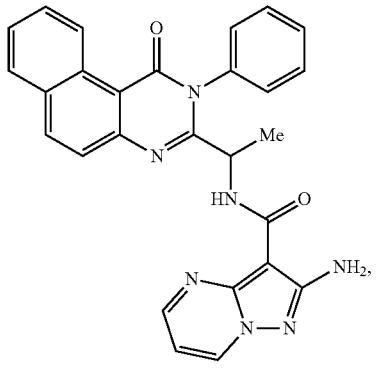
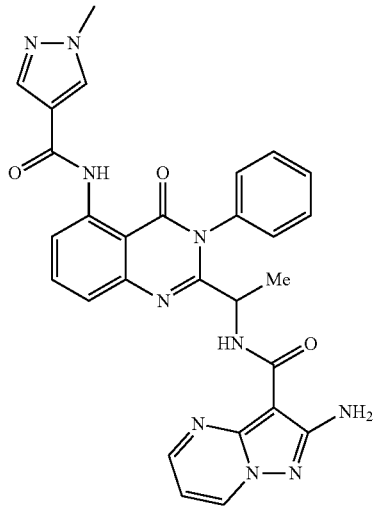


TABLE 9-continued

Compound 2089'



Compound 2090'



Compound 2091'

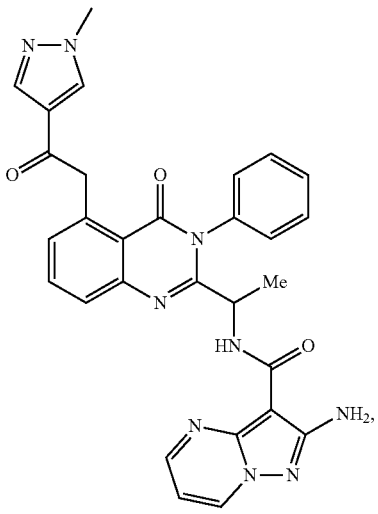
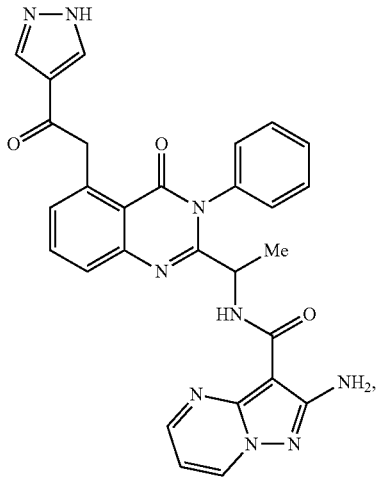
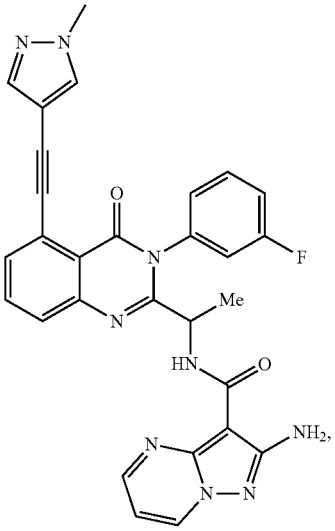


TABLE 9-continued

Compound 2092'



Compound 2093'



Compound 2094'

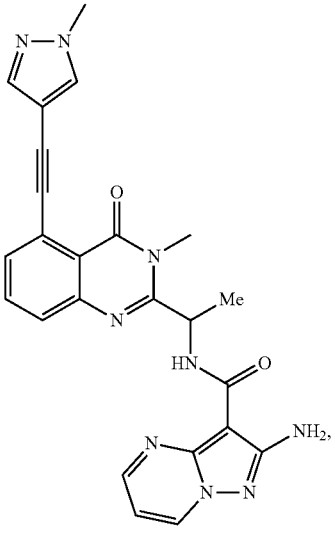
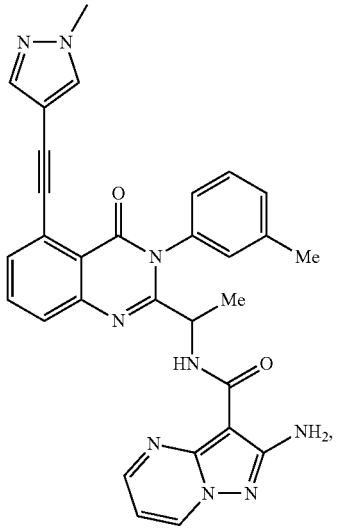
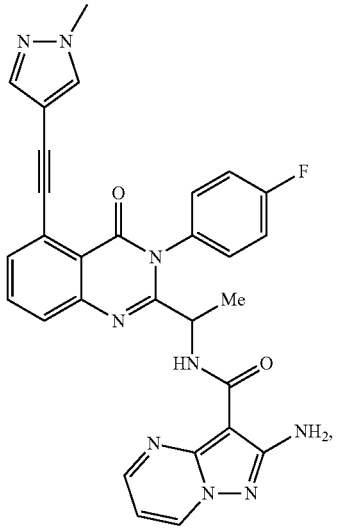


TABLE 9-continued

Compound 2095'



Compound 2096'



Compound 2097'

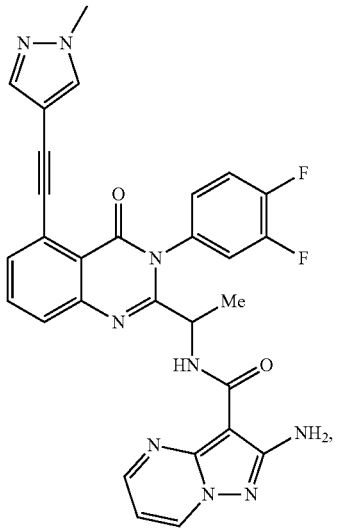
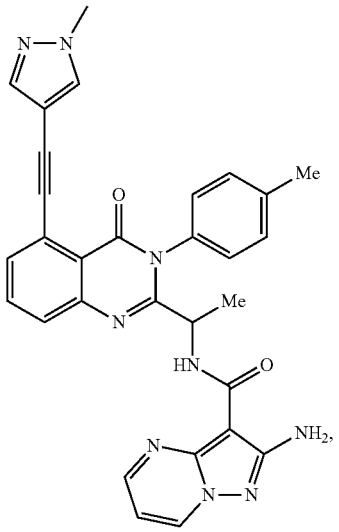
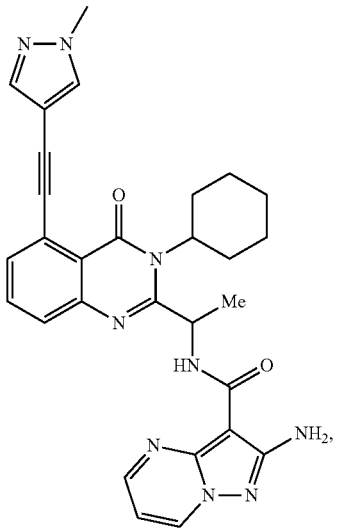


TABLE 9-continued

Compound 2098'



Compound 2099'



Compound 2100'

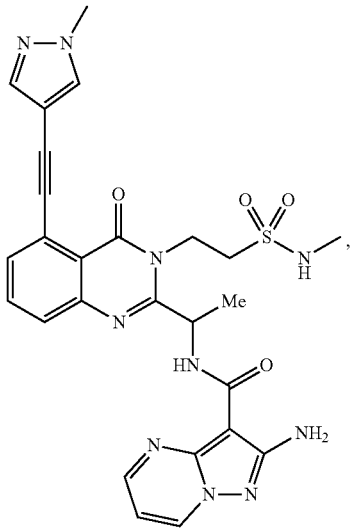
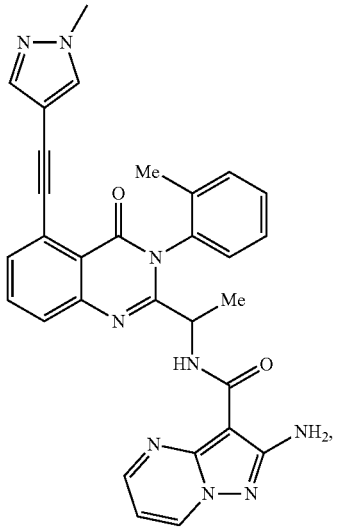
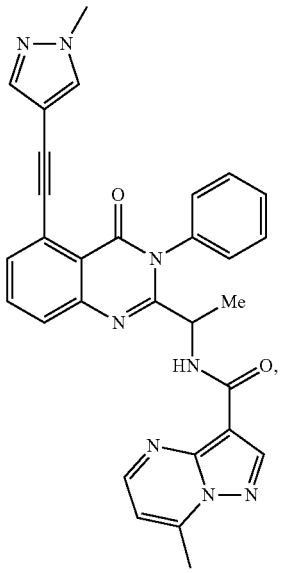


TABLE 9-continued

Compound 2101'



Compound 2102'



Compound 2103'

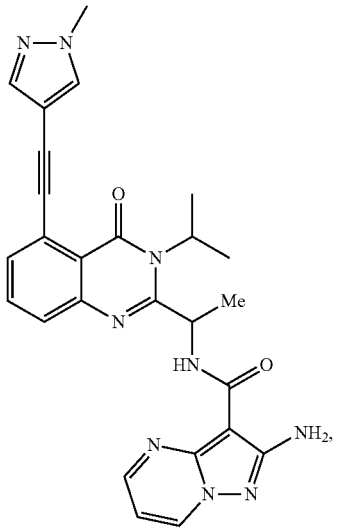
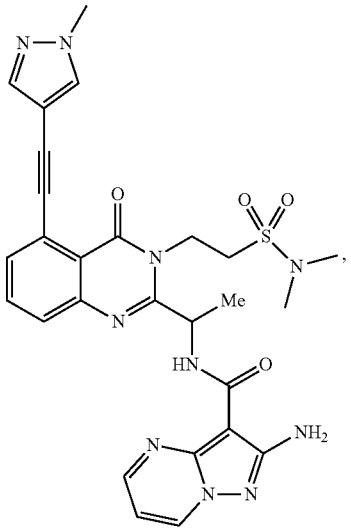
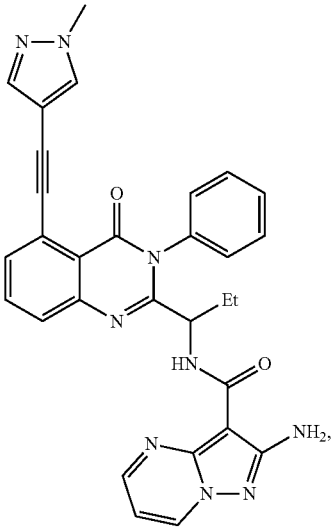


TABLE 9-continued

Compound 2104'



Compound 2105'



Compound 2106'

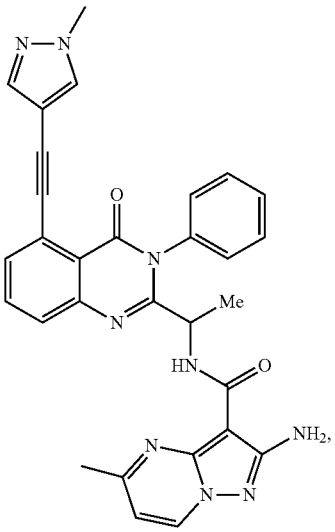
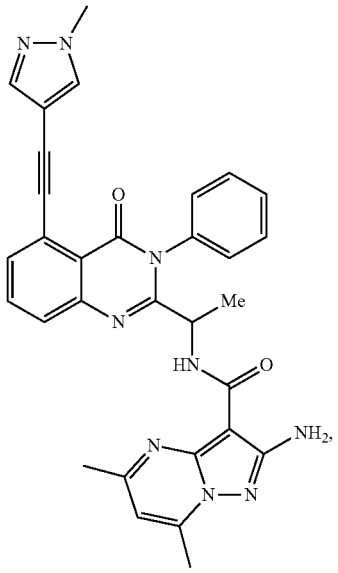


TABLE 9-continued

Compound 2108'



Compound 2109'

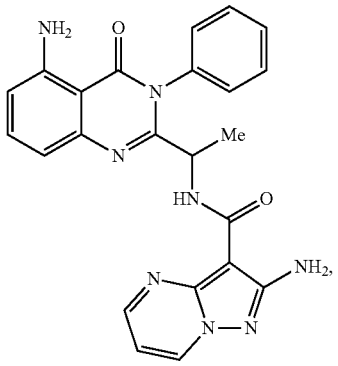


TABLE 10

Compound 3001'

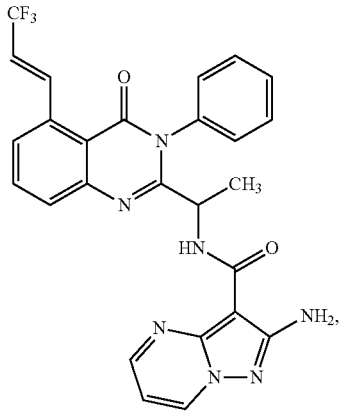
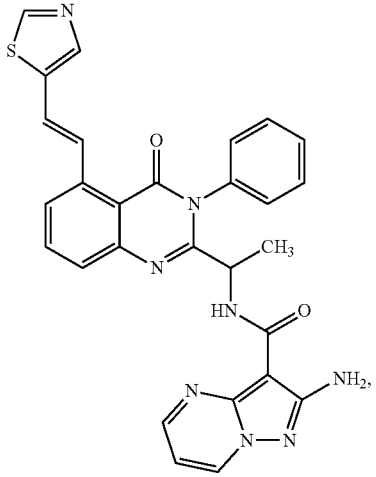
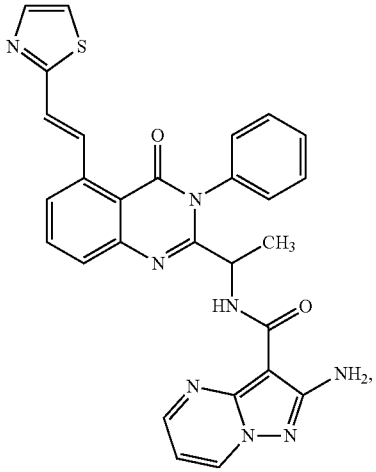


TABLE 10-continued

Compound 3002'



Compound 3003'



Compound 3004'

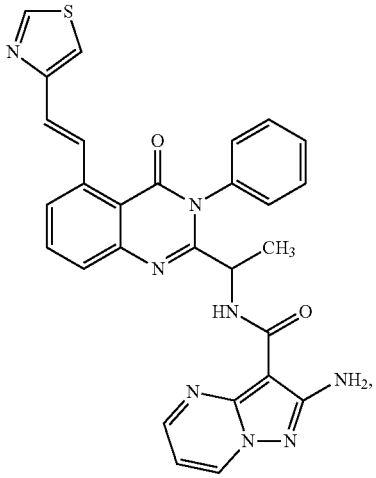
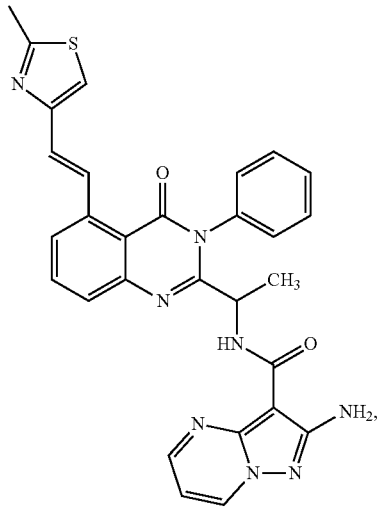
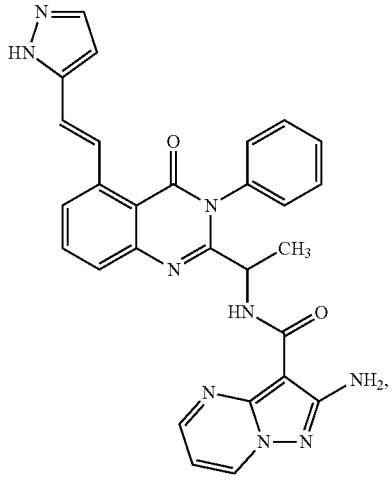


TABLE 10-continued

Compound 3005'



Compound 3006'



Compound 3007'

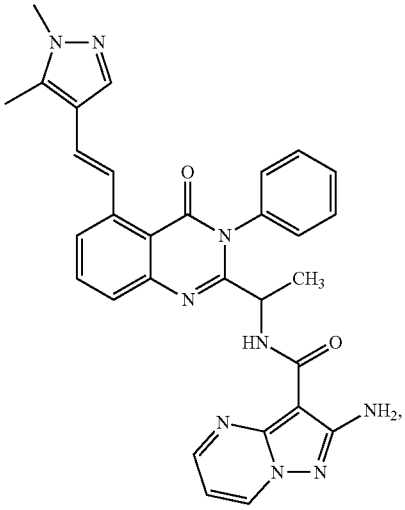
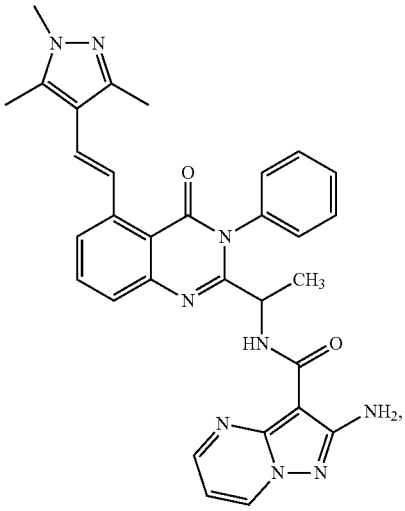
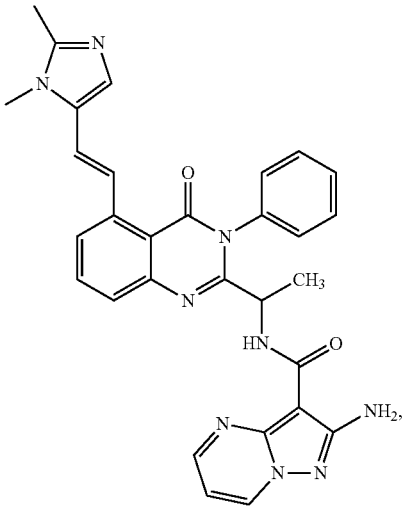


TABLE 10-continued

Compound 3008'



Compound 3009'



Compound 3010'

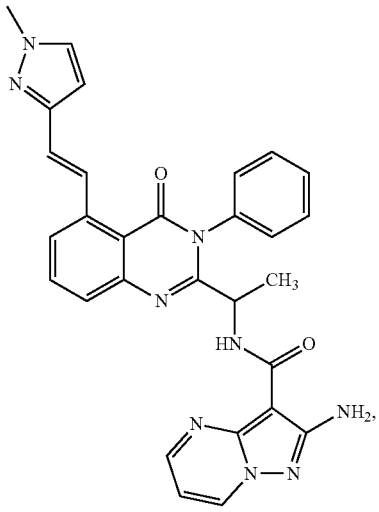
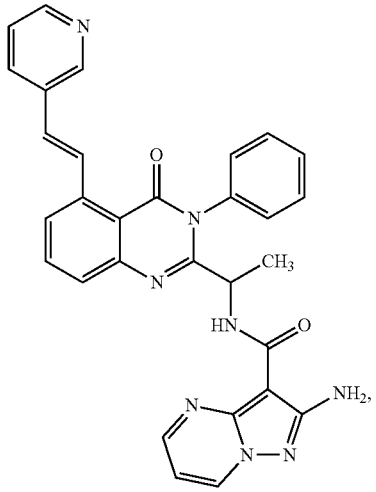
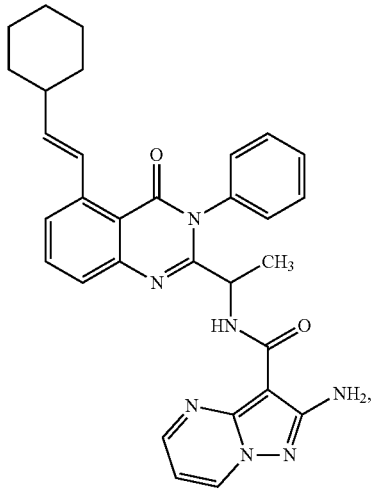


TABLE 10-continued

Compound 3011'



Compound 3012'



Compound 3013'

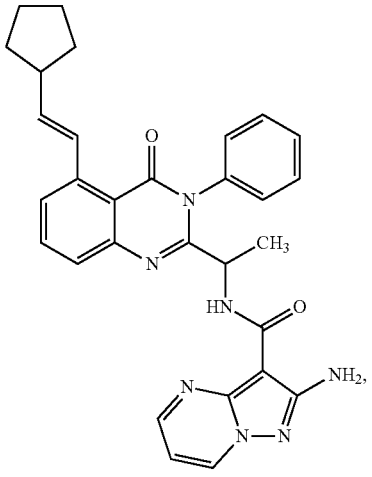
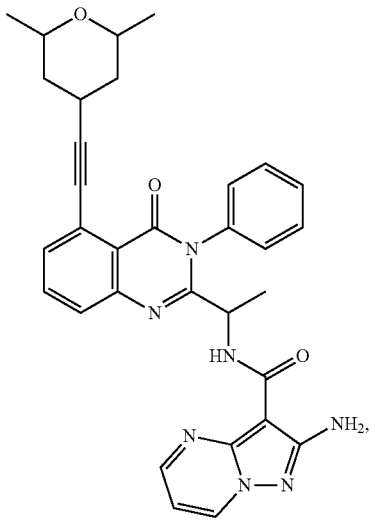
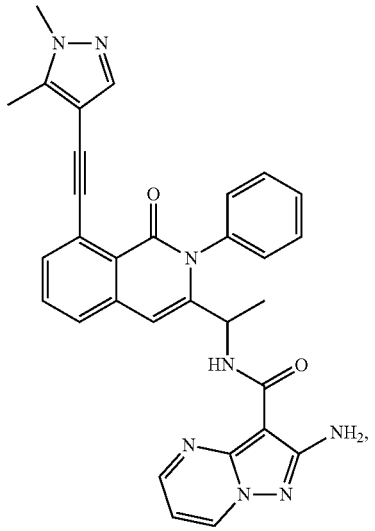


TABLE 10-continued

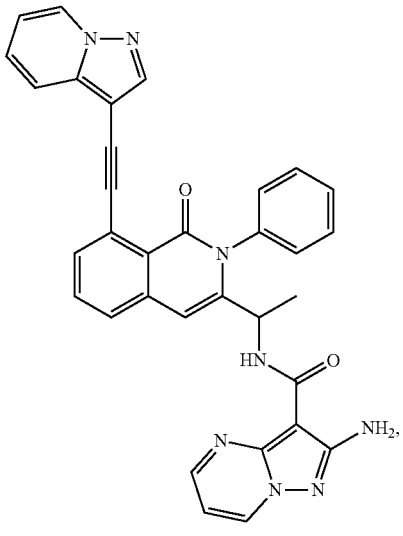
Compound 3014'



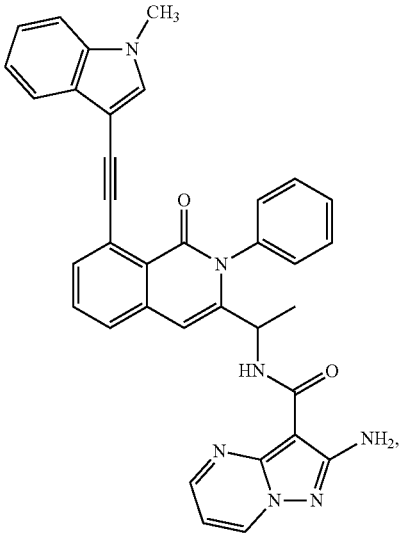
Compound 3015'



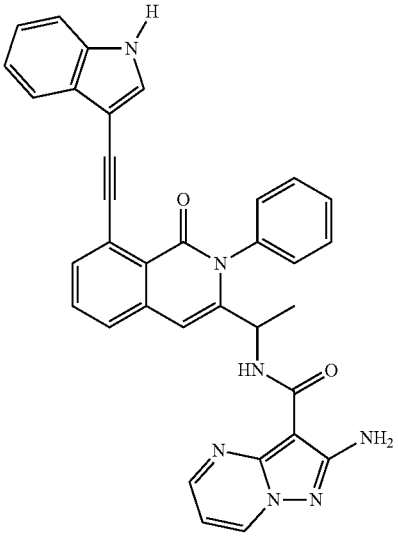
Compound 3016'



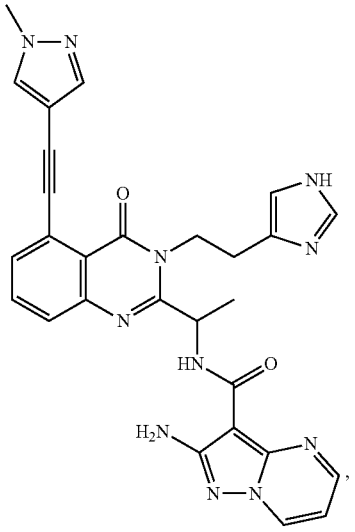
Compound 3017'



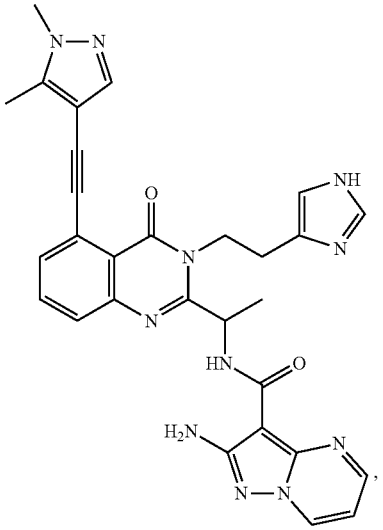
Compound 3018'



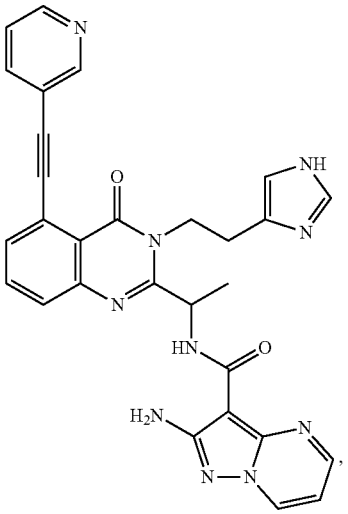
Compound 3045'



Compound 3046'



Compound 3047'



Compound 3048'

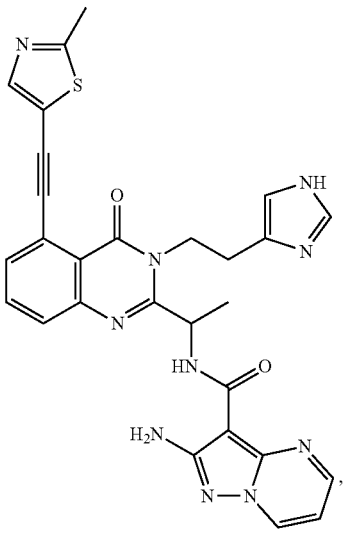


TABLE 10-continued

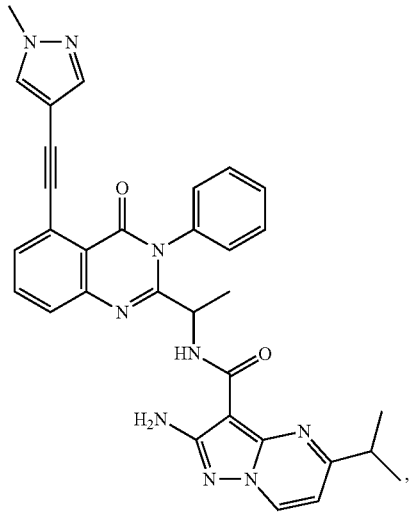
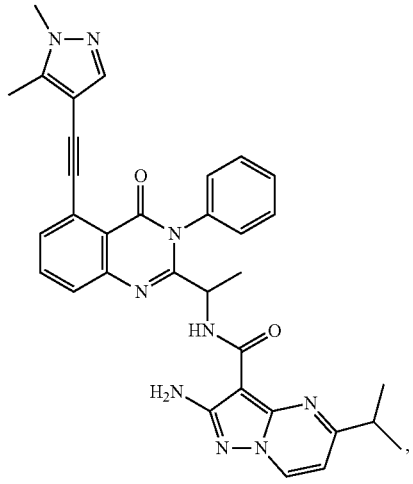
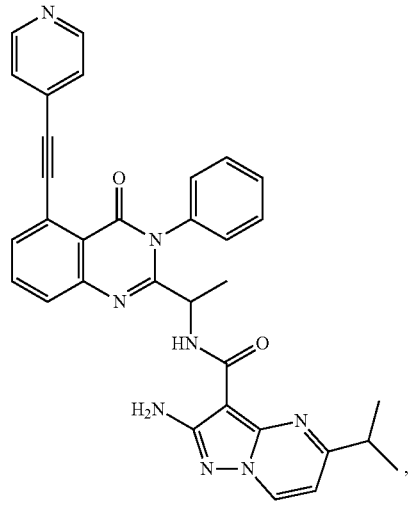
Compound 3049'	
Compound 3050'	
Compound 3051'	

TABLE 10-continued

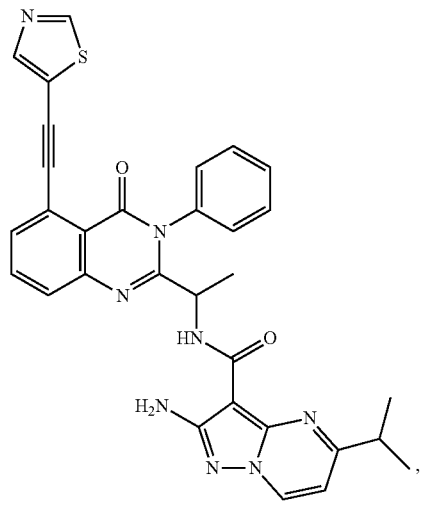
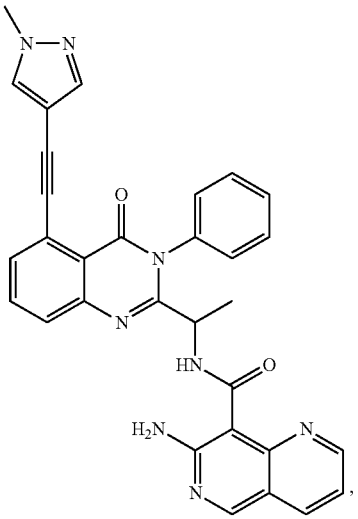
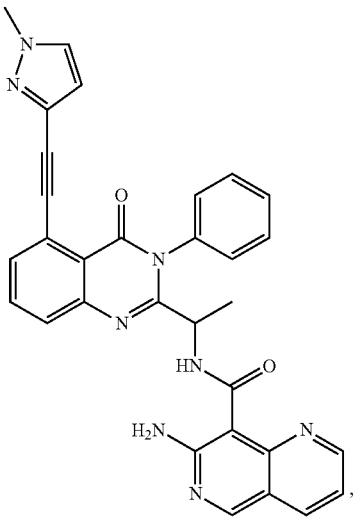
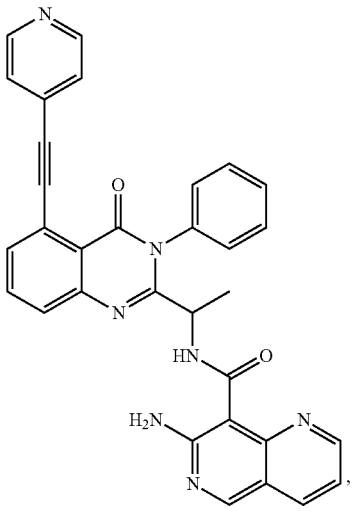
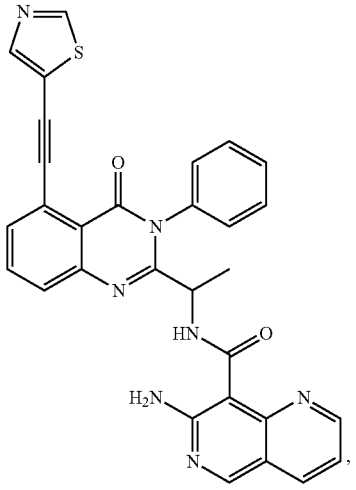
Compound 3052'	
Compound 3053'	
Compound 3054'	

TABLE 10-continued

Compound 3055'



Compound 3056'



Compound 3057'

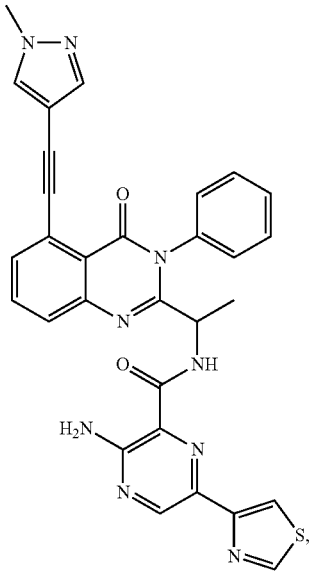
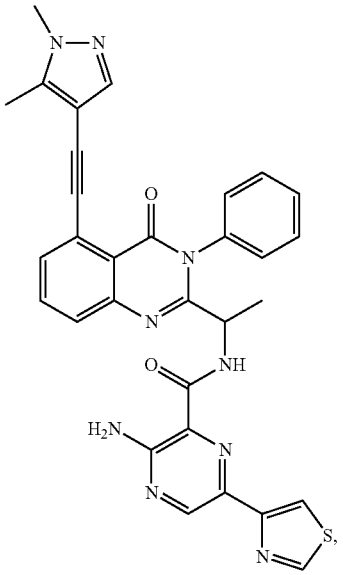


TABLE 10-continued

Compound 3058'



Compound 3059'

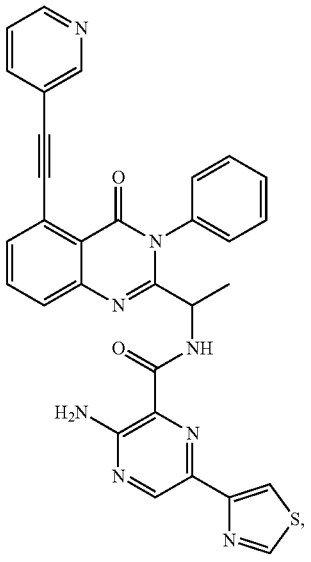
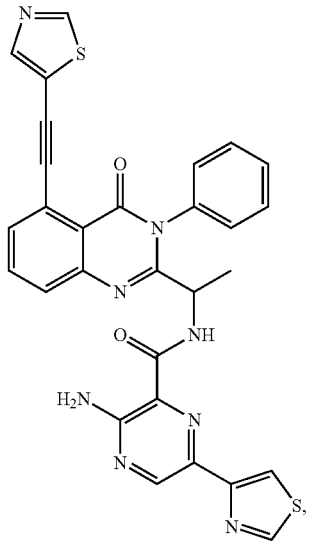
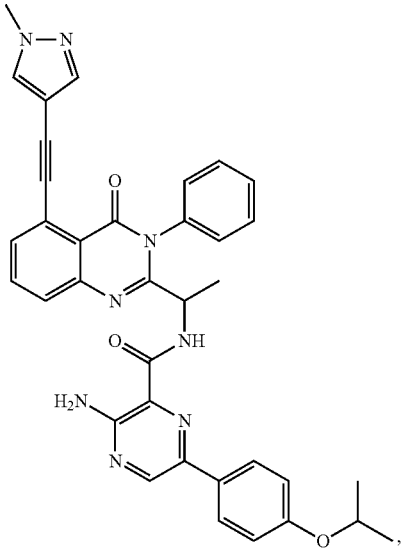


TABLE 10-continued

Compound 3060'



Compound 3061'



Compound 3062'

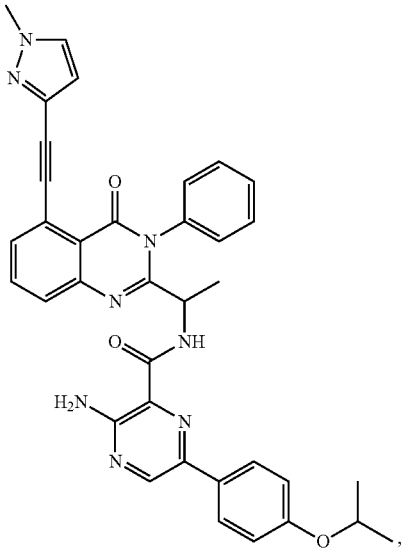
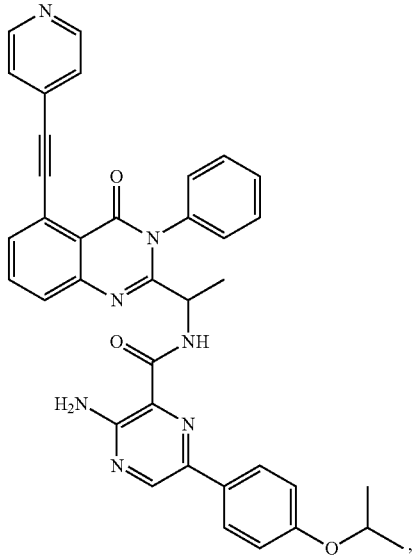


TABLE 10-continued

Compound 3063'



Compound 3064'

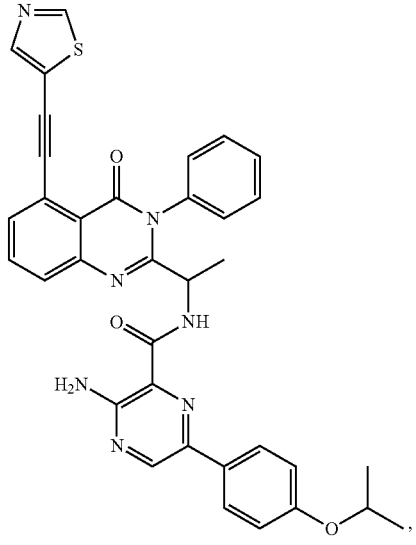
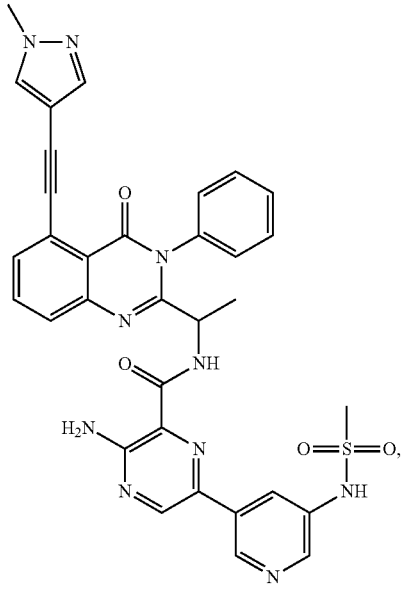


TABLE 10-continued

Compound 3065'



Compound 3066'

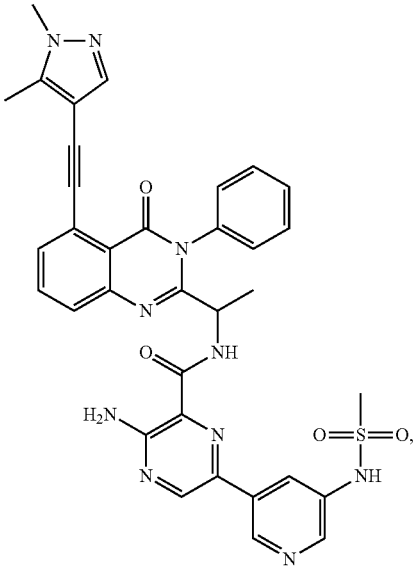
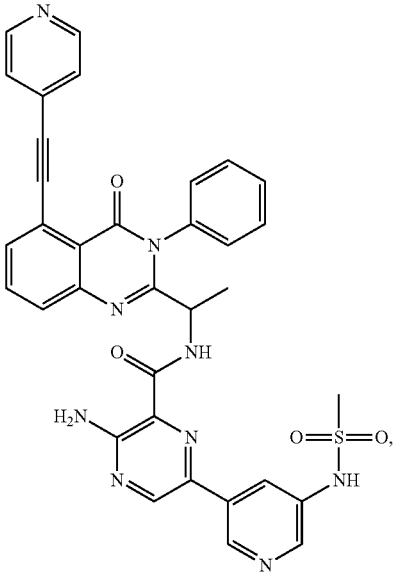


TABLE 10-continued

Compound 3067'



Compound 3068'

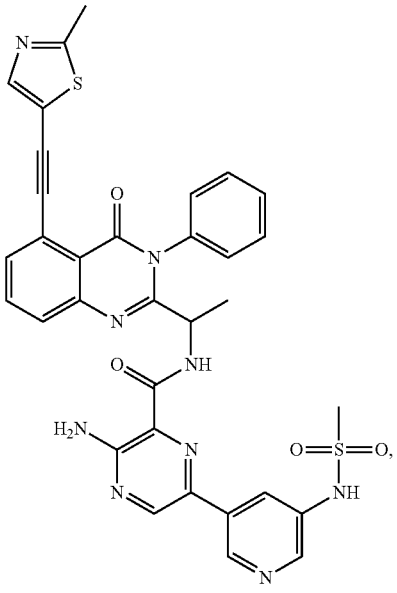
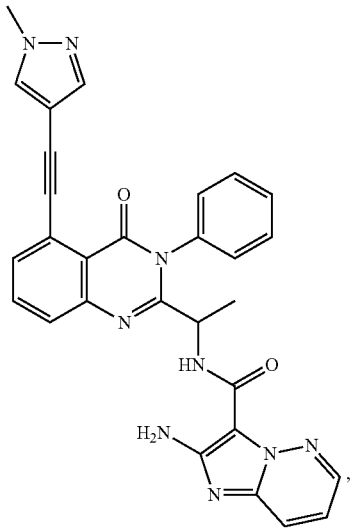
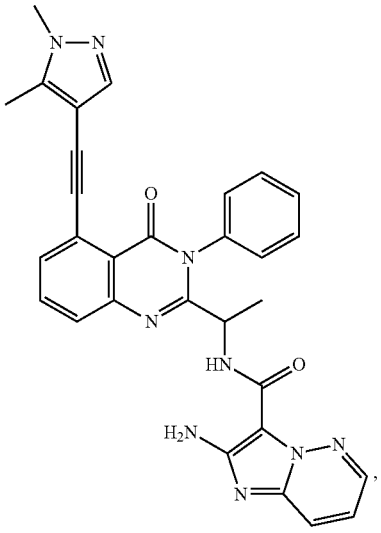


TABLE 10-continued

Compound 3069'



Compound 3070'



Compound 3071'

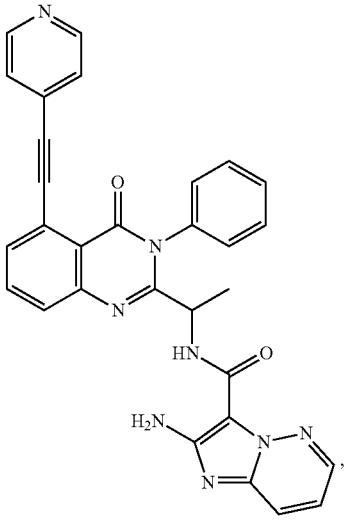
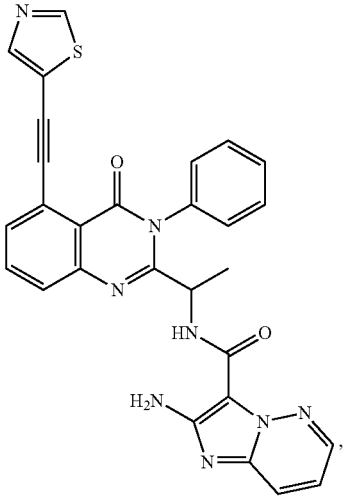
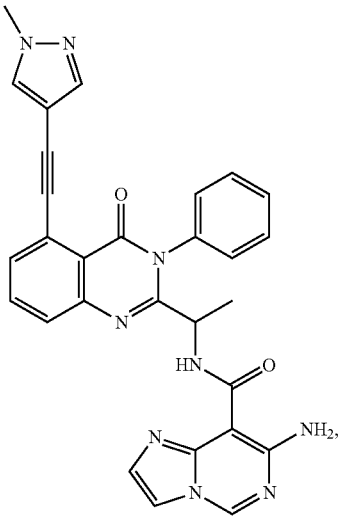


TABLE 10-continued

Compound 3072'



Compound 3073'



Compound 3074'

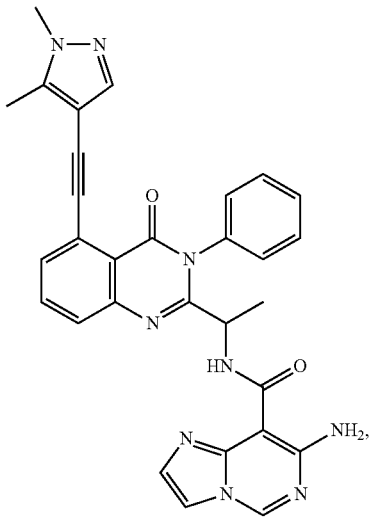


TABLE 10-continued

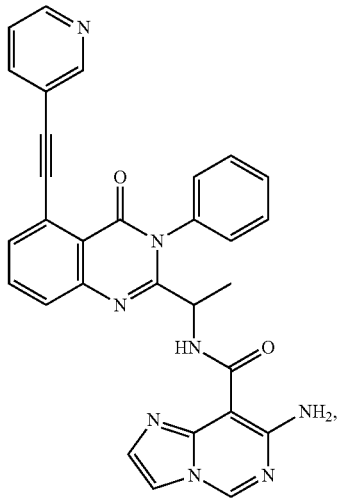
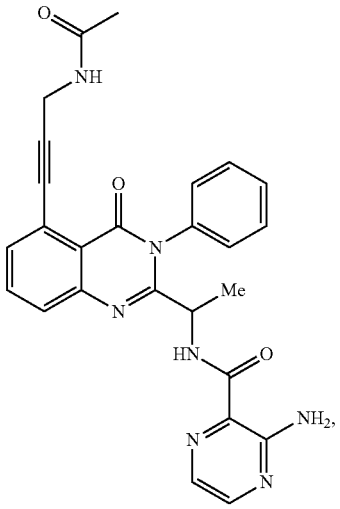
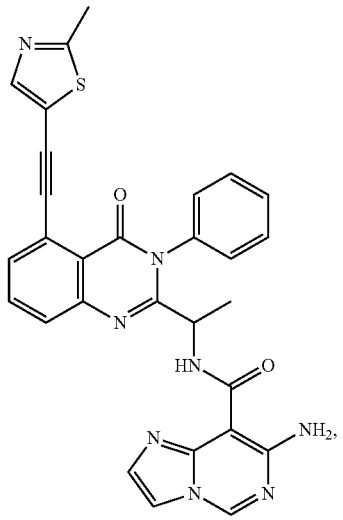
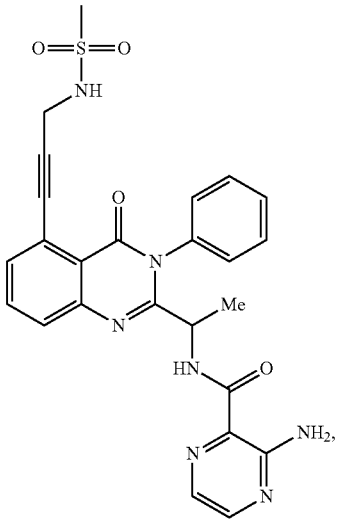
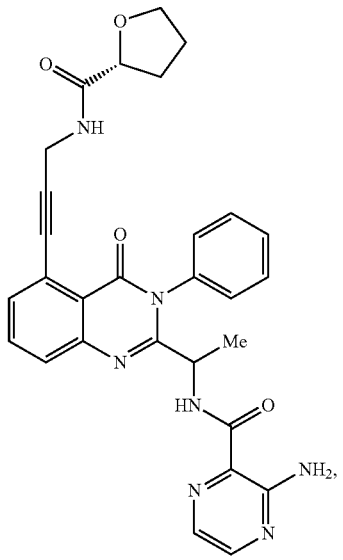
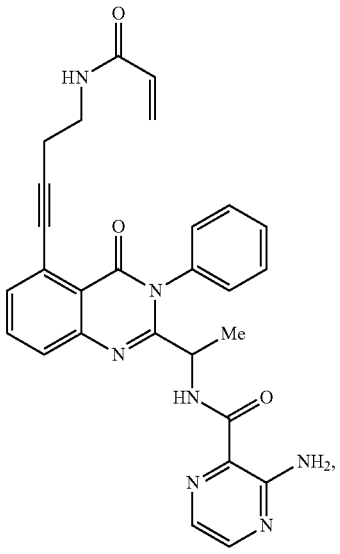
Compound 3075' 	Compound 3078' 
Compound 3076' 	Compound 3079' 
Compound 3077' 	Compound 3080' 

TABLE 10-continued

TABLE 10-continued

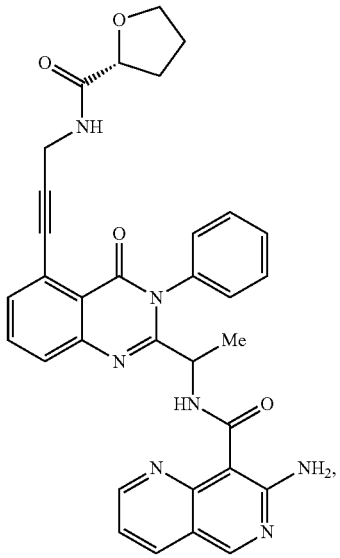
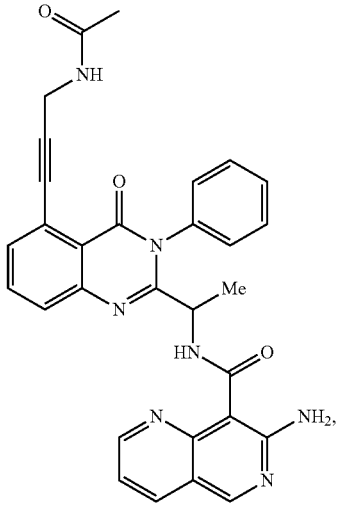
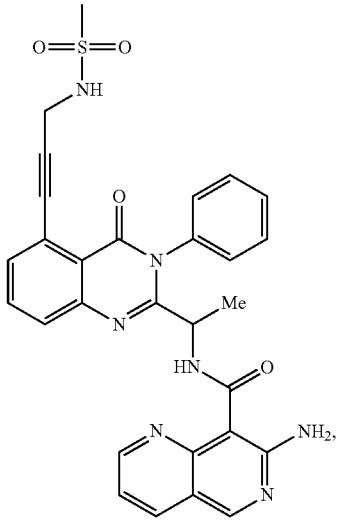
Compound 3081'	
Compound 3082'	
Compound 3083'	

TABLE 10-continued

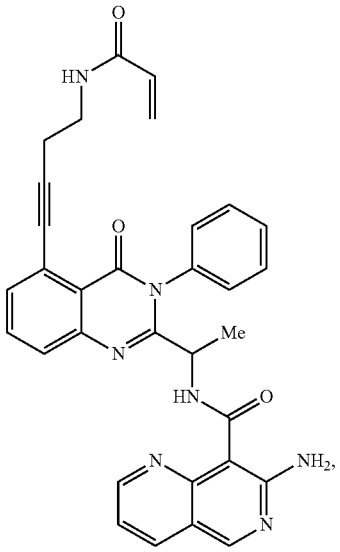
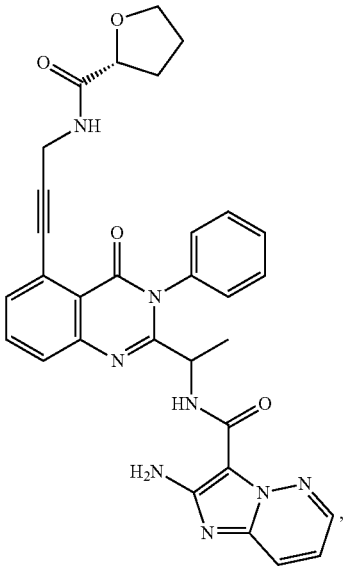
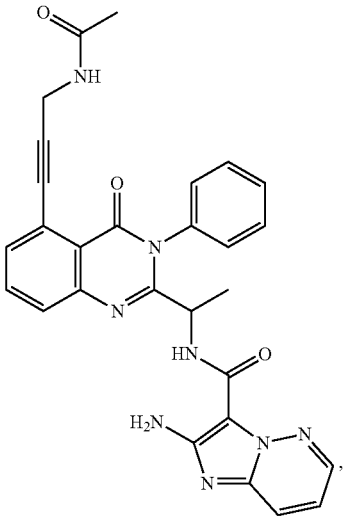
Compound 3084'	
Compound 3085'	
Compound 3086'	

TABLE 10-continued

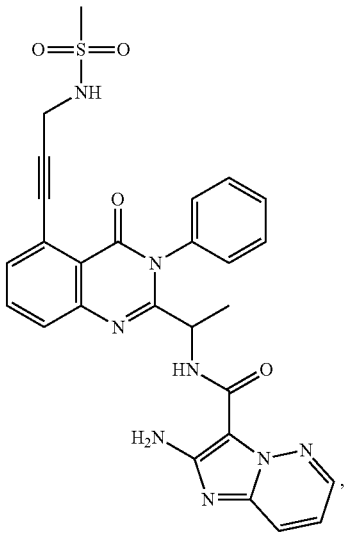
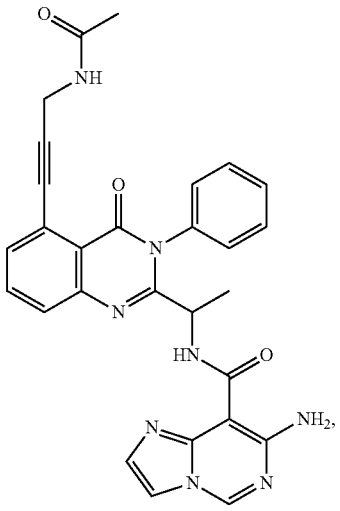
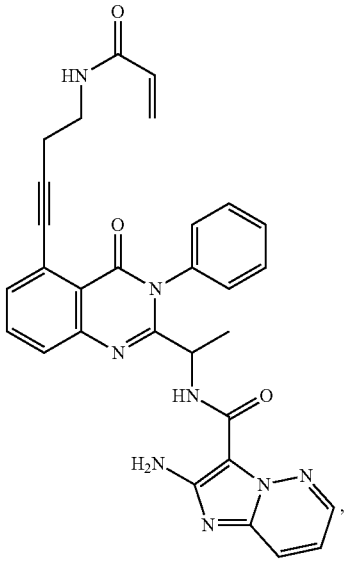
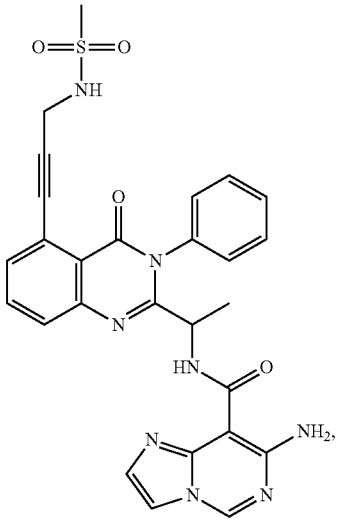
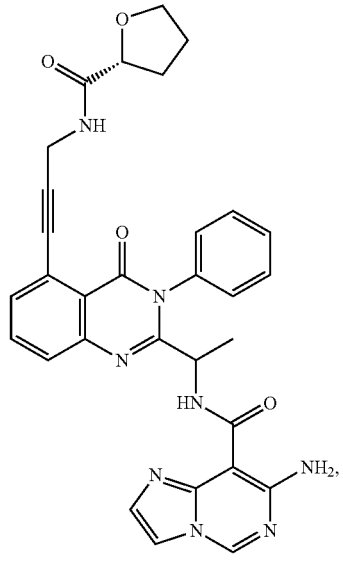
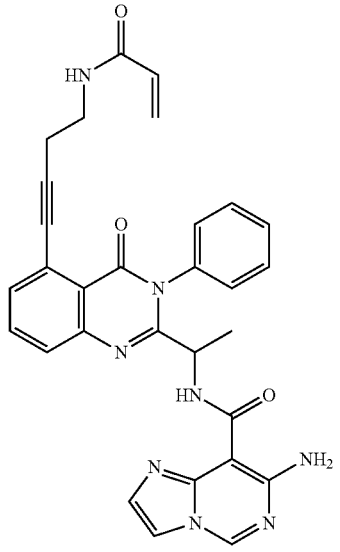
Compound 3087' 	Compound 3090' 
Compound 3088' 	Compound 3091' 
Compound 3089' 	Compound 3092' 

TABLE 10-continued

TABLE 11

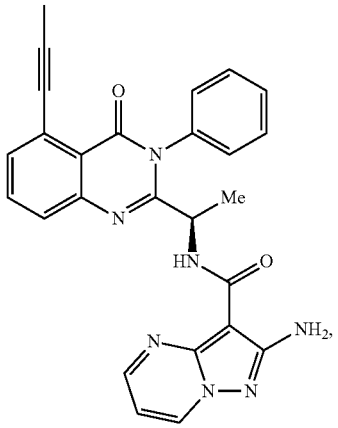
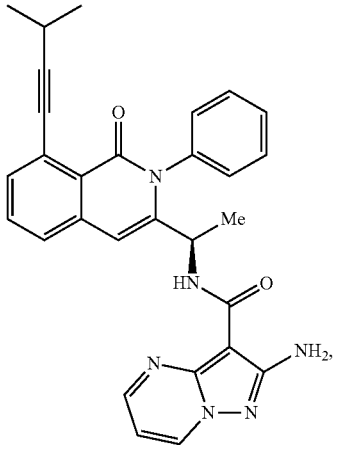
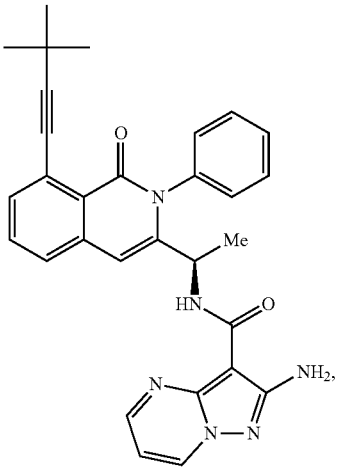
Compound 1r	
Compound 2r	
Compound 3r	

TABLE 11-continued

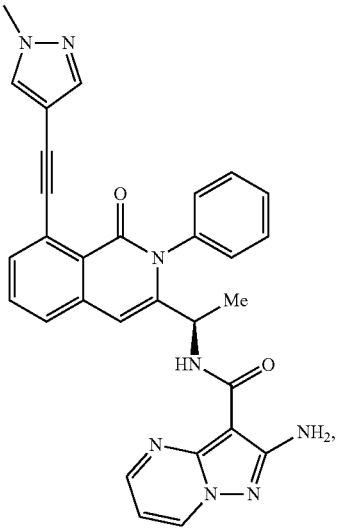
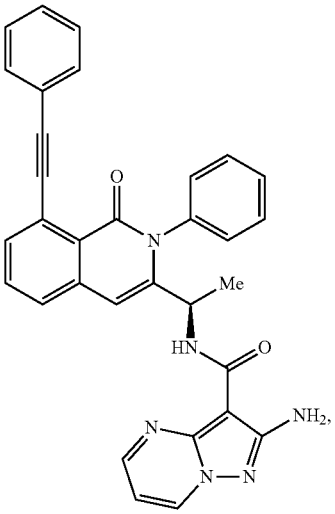
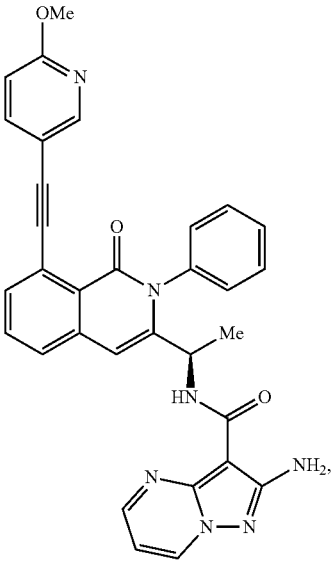
Compound 4r	
Compound 5r	
Compound 6r	

TABLE 11-continued

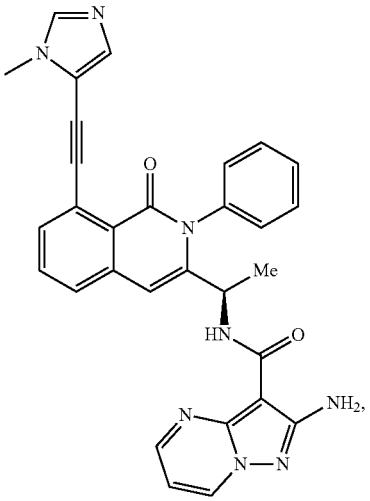
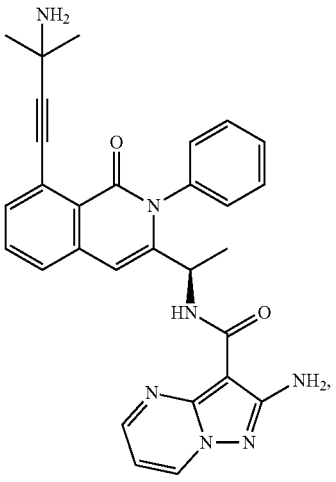
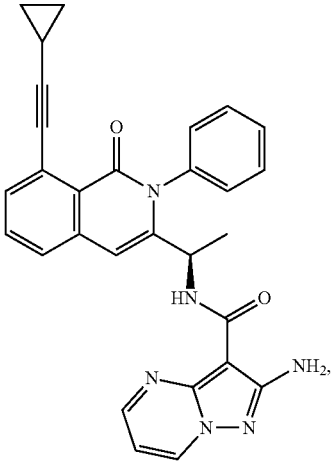
Compound 7r	
Compound 8r	
Compound 9r	

TABLE 11-continued

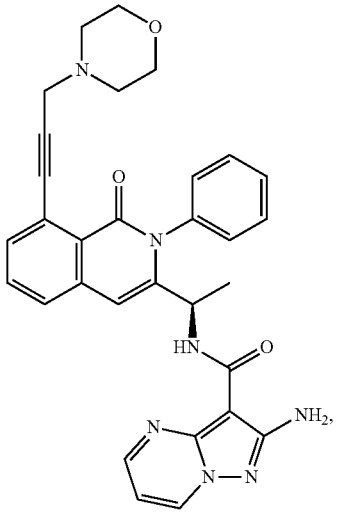
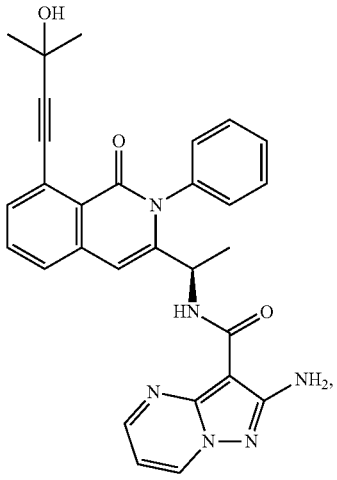
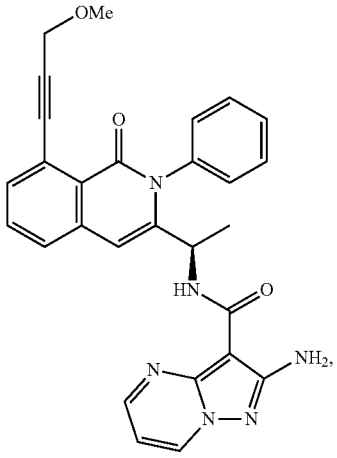
Compound 10r	
Compound 11r	
Compound 12r	

TABLE 11-continued

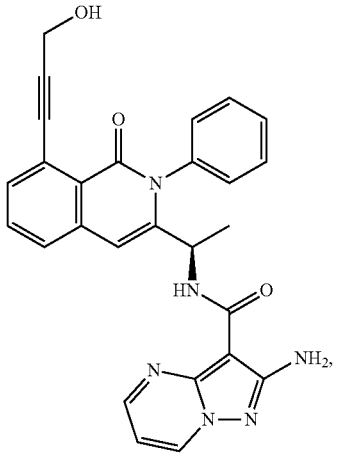
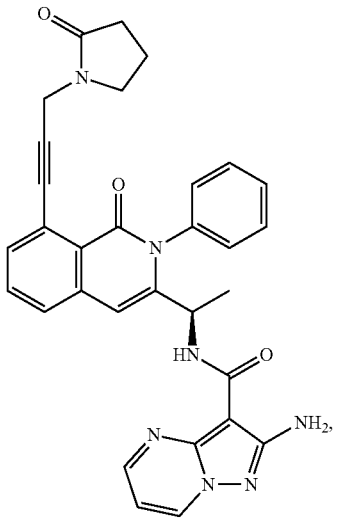
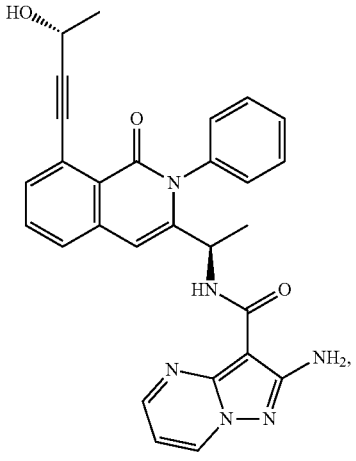
Compound 13r	
Compound 14r	
Compound 15r	

TABLE 11-continued

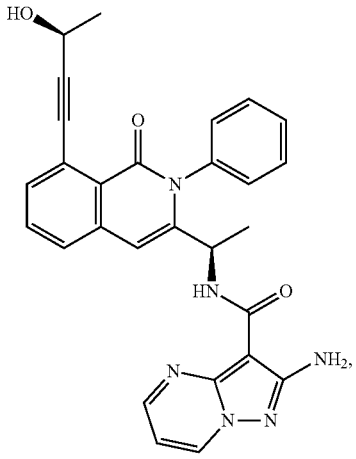
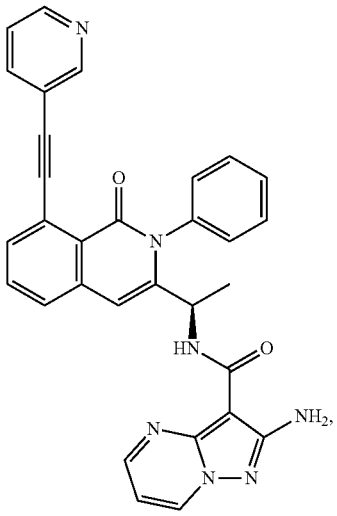
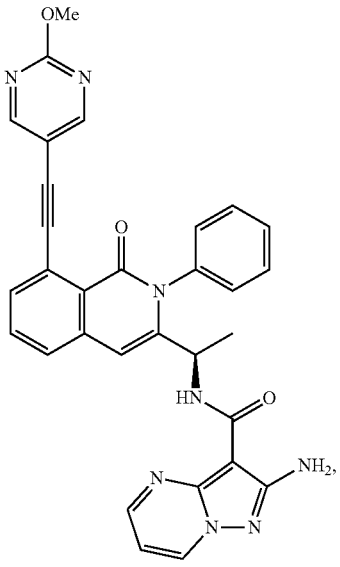
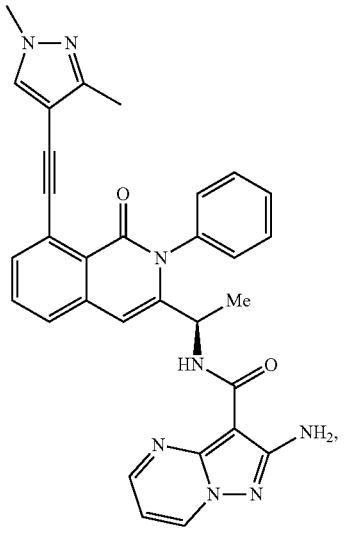
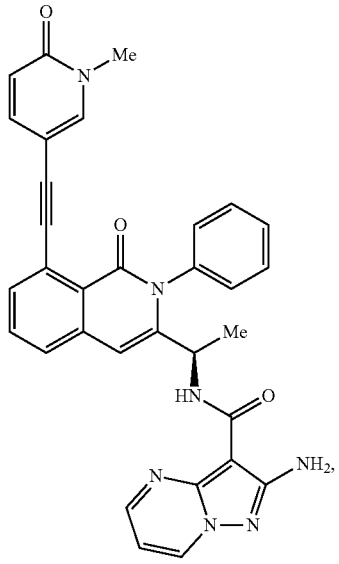
Compound 16r	
Compound 17r	
Compound 18r	

TABLE 11-continued

Compound 19r



Compound 20r



Compound 21r

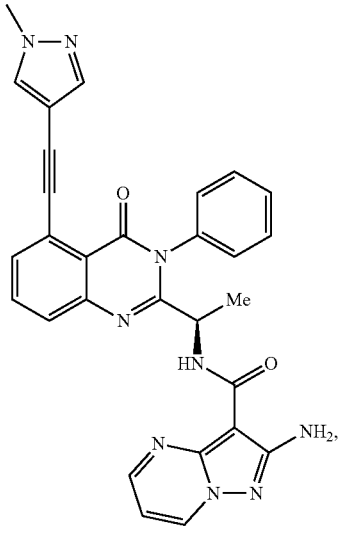
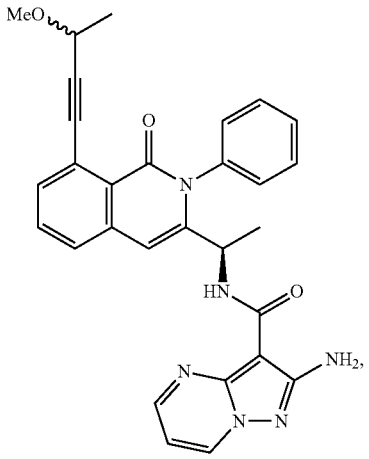
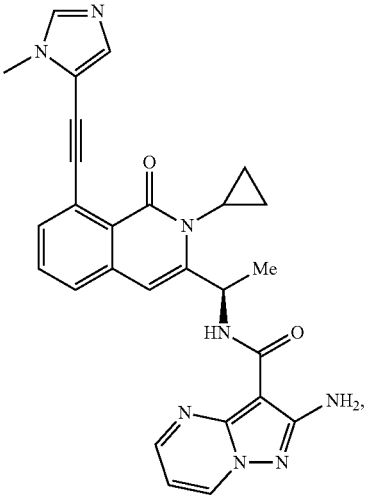


TABLE 11-continued

Compound 22r



Compound 23r



Compound 24r

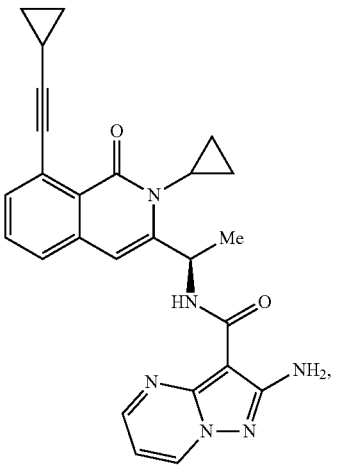


TABLE 11-continued

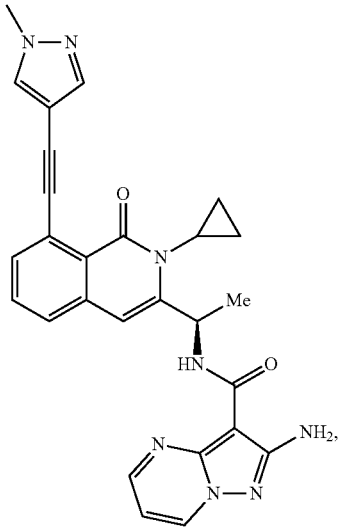
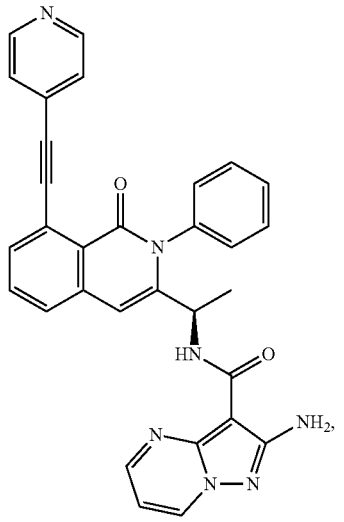
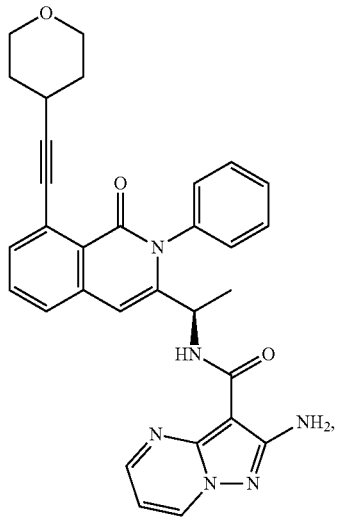
Compound 25r	
Compound 26r	
Compound 27r	

TABLE 11-continued

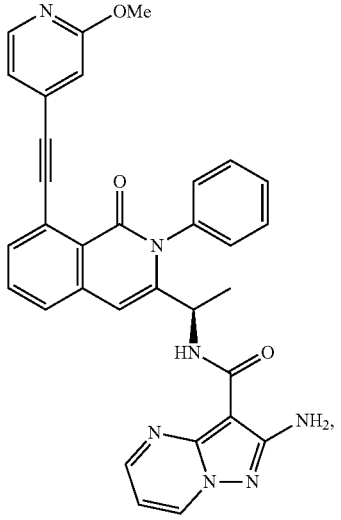
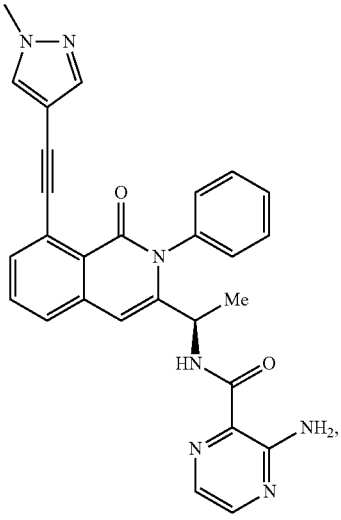
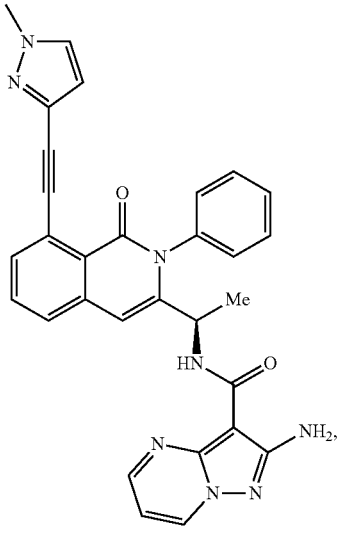
Compound 28r	
Compound 29r	
Compound 30r	

TABLE 11-continued

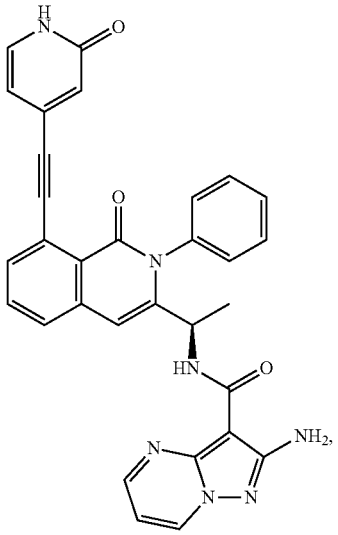
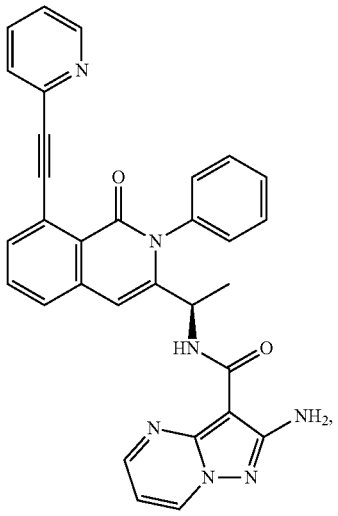
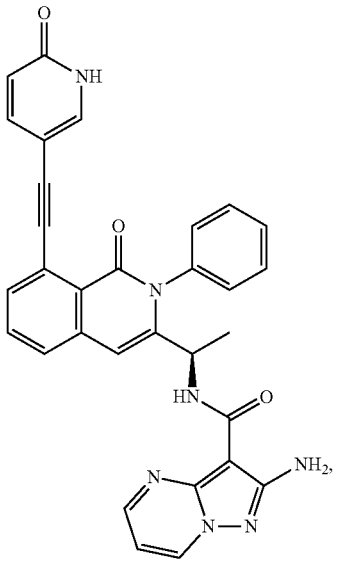
Compound 31r	
Compound 32r	
Compound 33r	

TABLE 11-continued

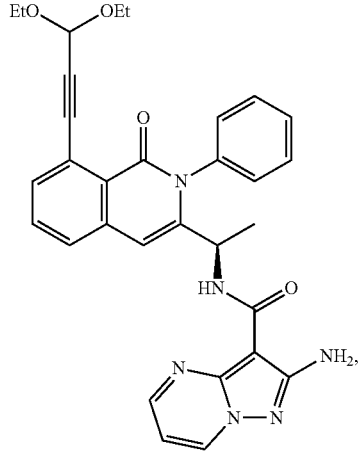
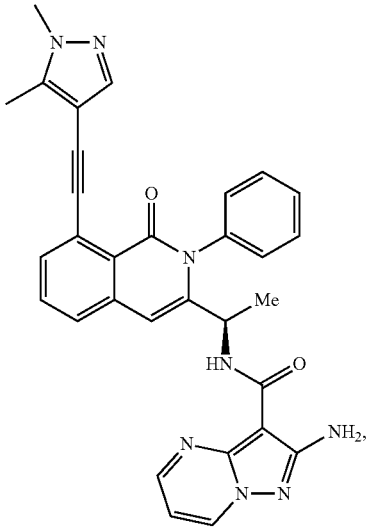
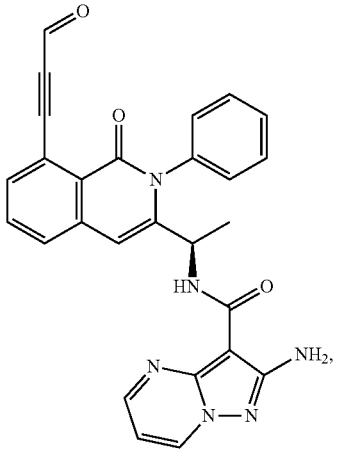
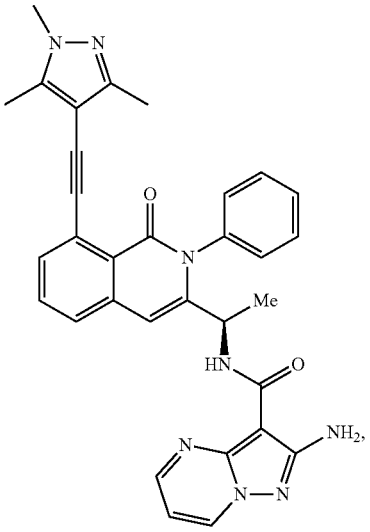
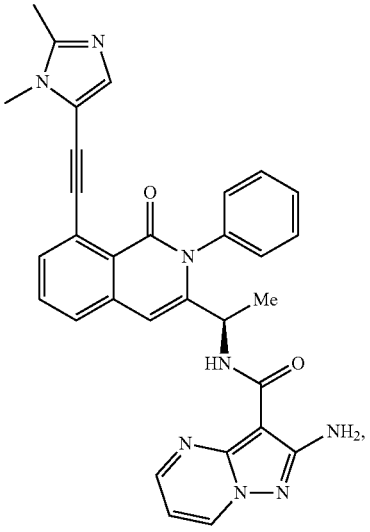
Compound 34r	
Compound 35r	
Compound 36r	

TABLE 11-continued

Compound 37r



Compound 38r



Compound 39r

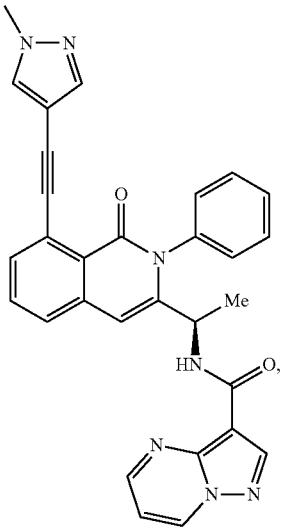
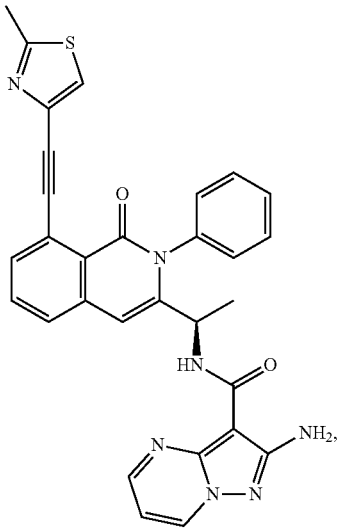
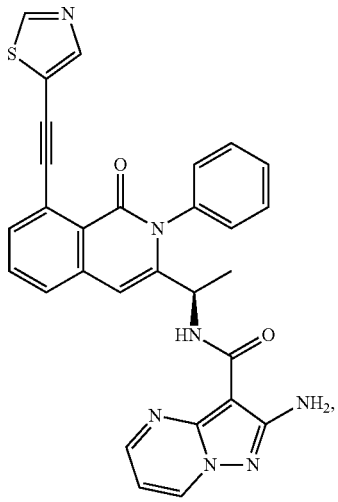


TABLE 11-continued

Compound 40r



Compound 41r



Compound 42r

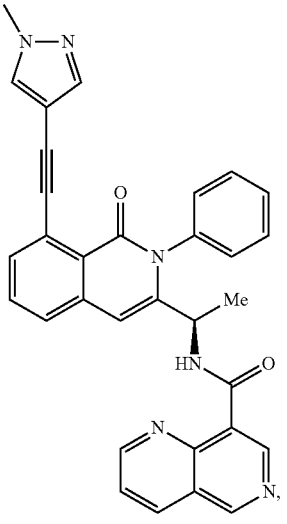


TABLE 11-continued

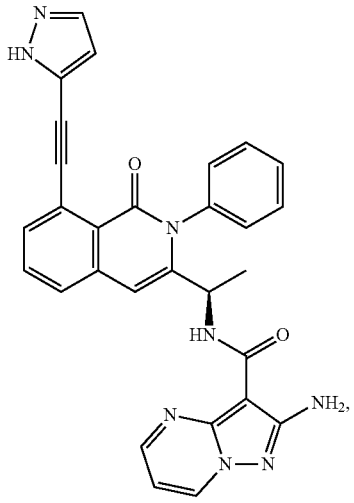
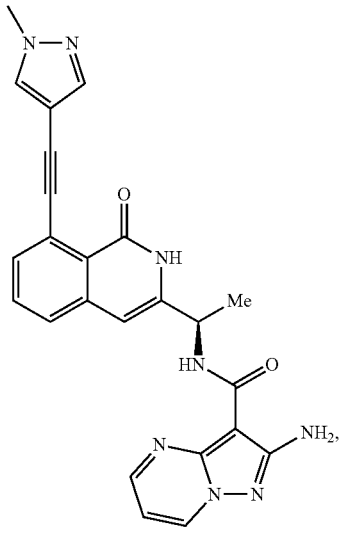
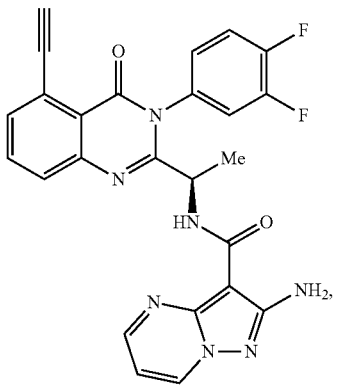
Compound 43r	
Compound 44r	
Compound 45r	

TABLE 11-continued

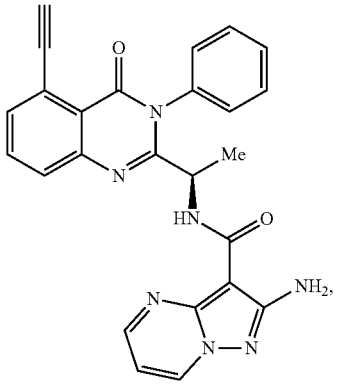
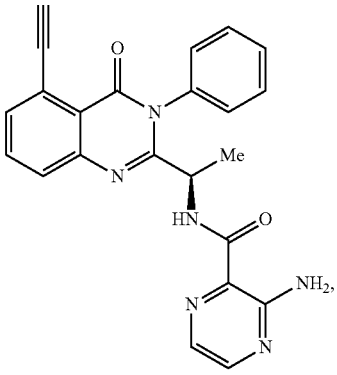
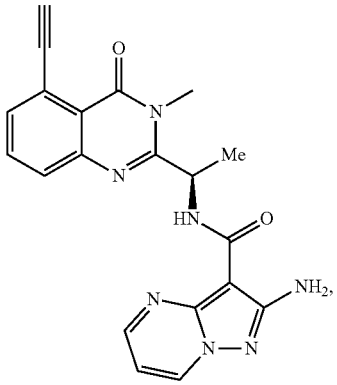
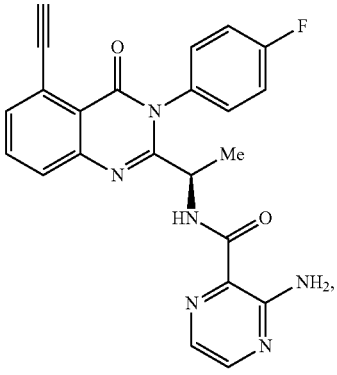
Compound 46r	
Compound 47r	
Compound 48r	
Compound 49r	

TABLE 11-continued

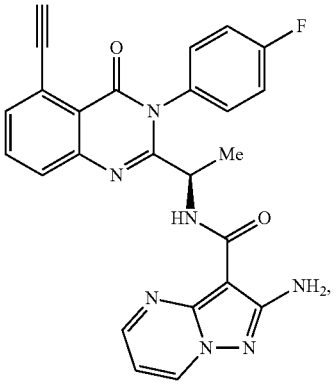
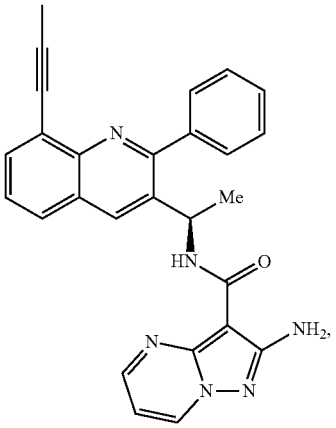
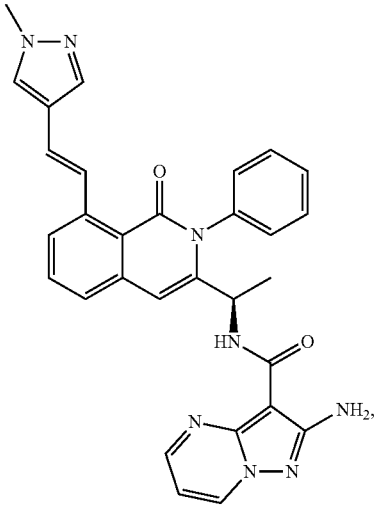
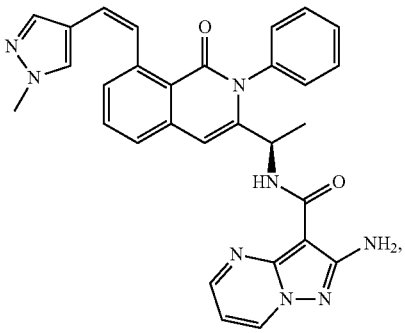
Compound 50r	
Compound 51r	
Compound 52r	
Compound 53r	

TABLE 11-continued

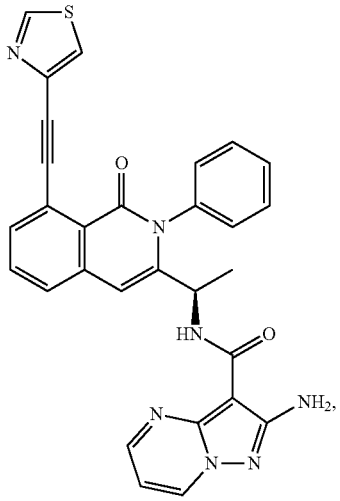
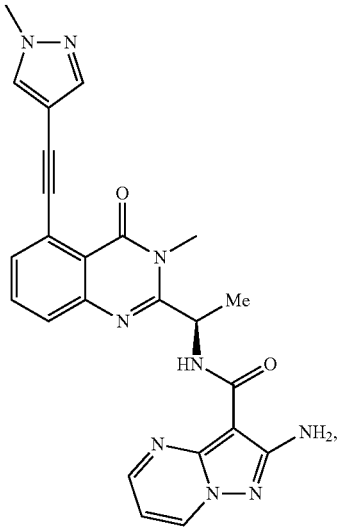
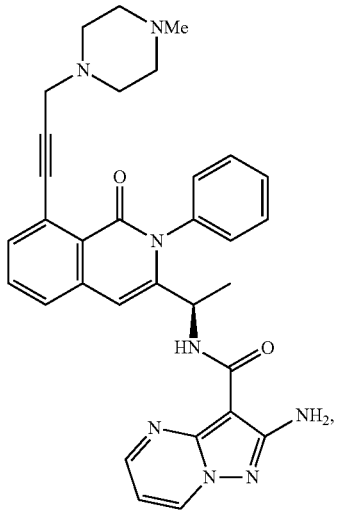
Compound 54r	
Compound 55r	
Compound 56r	

TABLE 11-continued

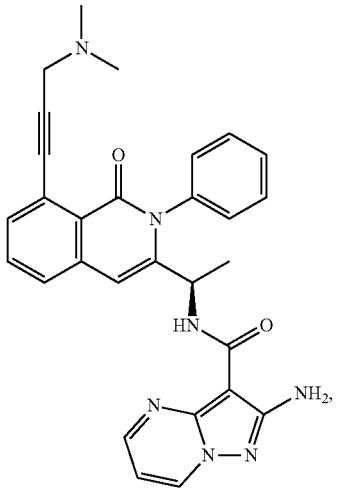
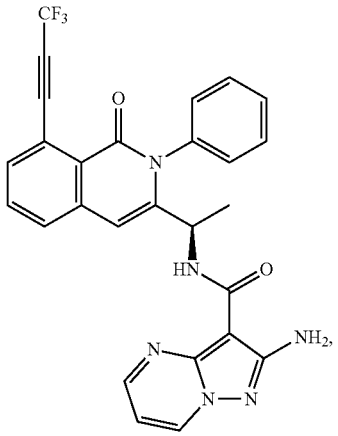
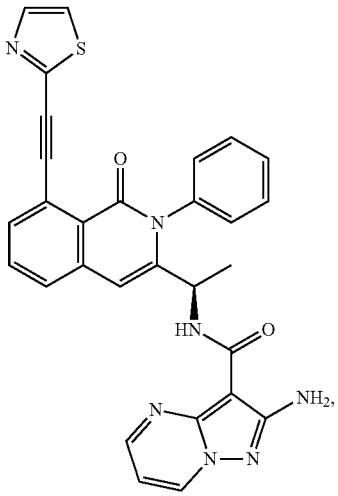
Compound 57r	
Compound 58r	
Compound 59r	

TABLE 11-continued

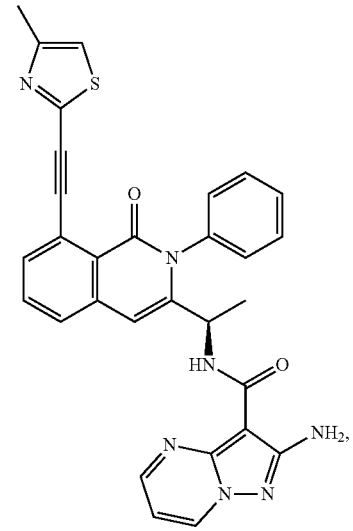
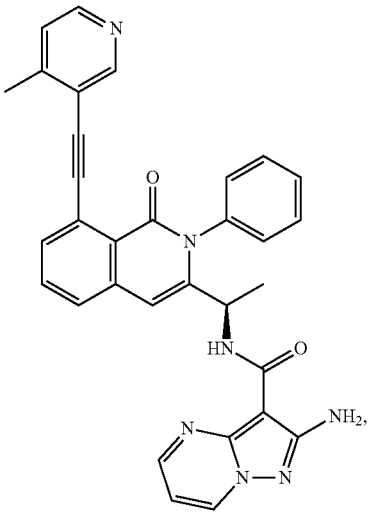
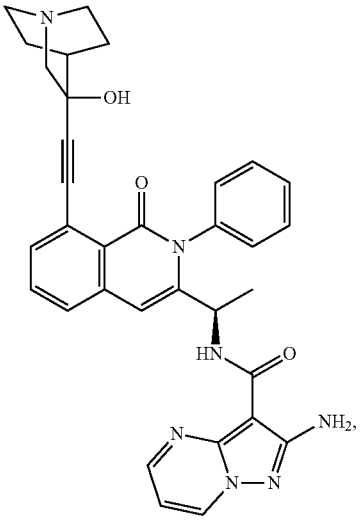
Compound 60r	
Compound 61r	
Compound 62r	

TABLE 11-continued

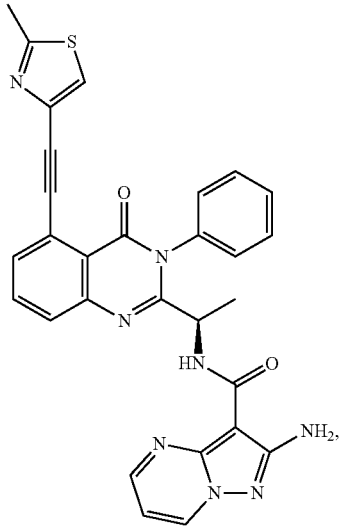
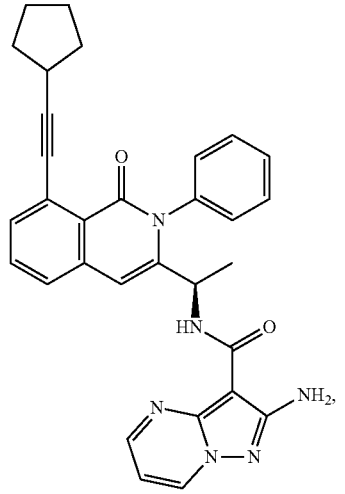
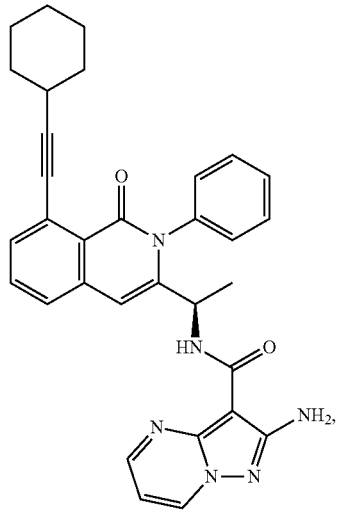
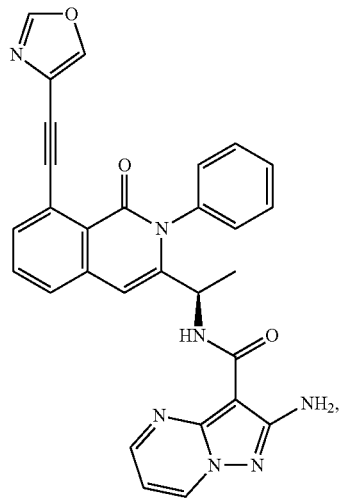
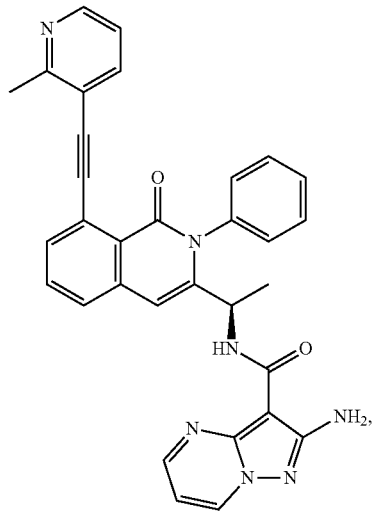
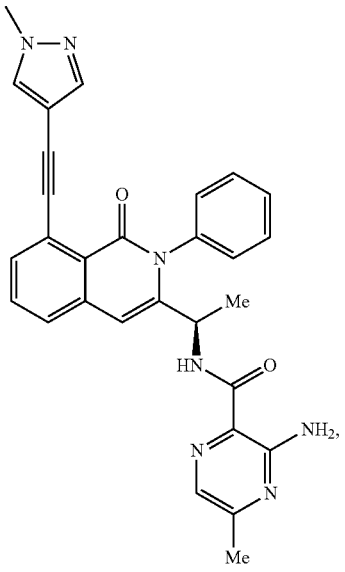
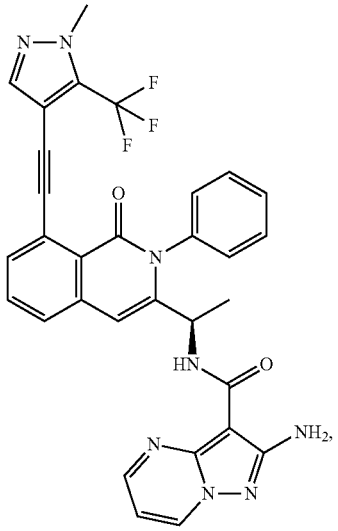
Compound 63r	
Compound 64r	
Compound 65r	

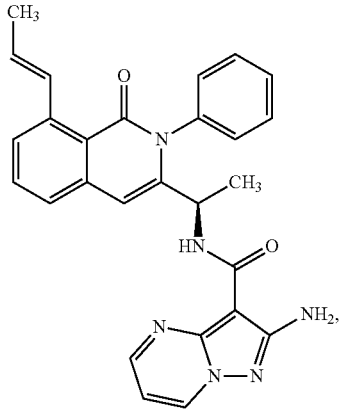
TABLE 11-continued

Compound 66r	
Compound 67r	
Compound 68r	

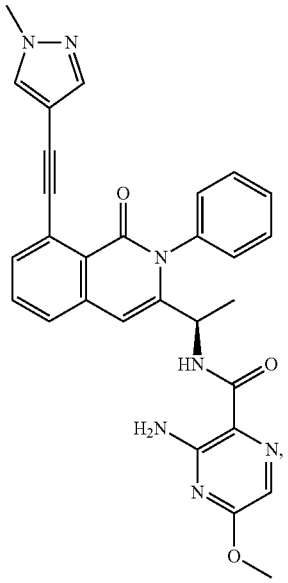
Compound 69r



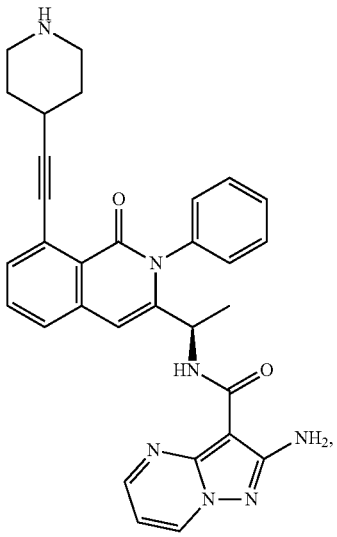
Compound 70r



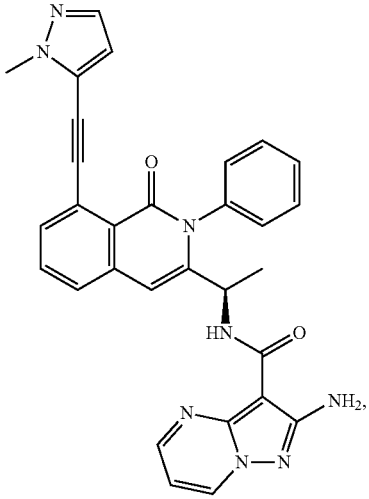
Compound 71r



Compound 72r



Compound 73r



Compound 74r

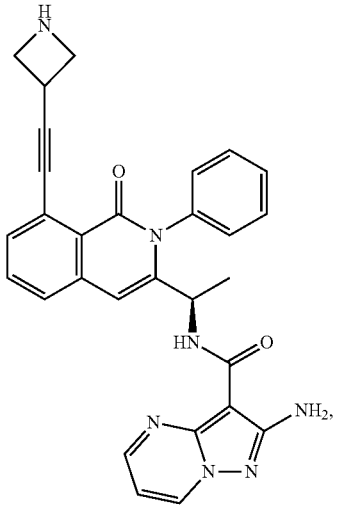


TABLE 11-continued

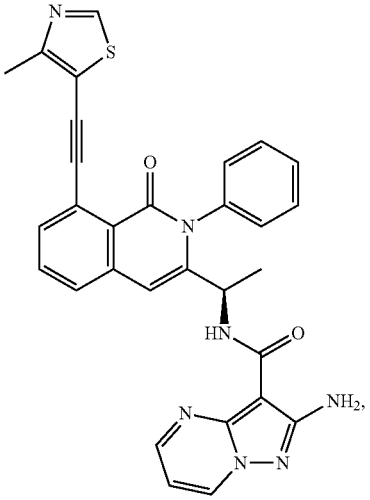
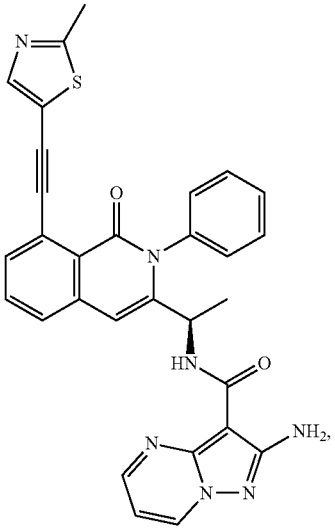
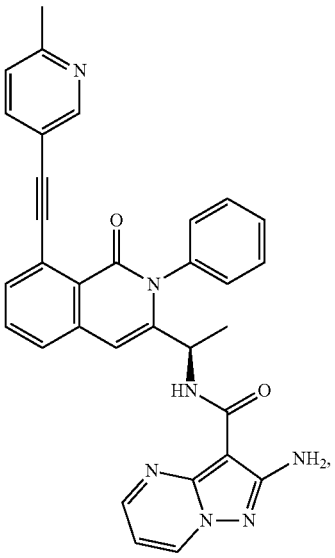
Compound 75r	
Compound 76r	
Compound 77r	

TABLE 11-continued

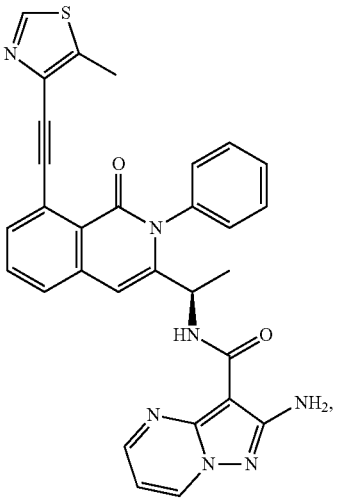
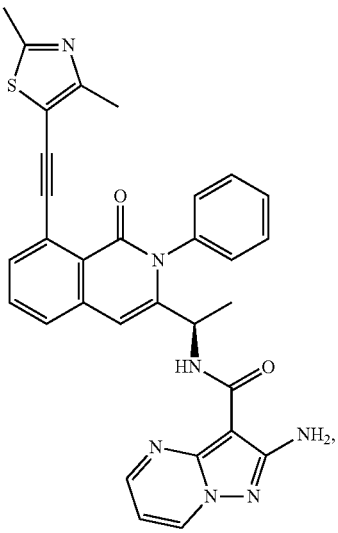
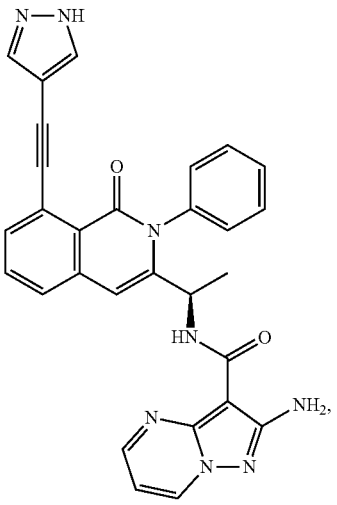
Compound 78r	
Compound 79r	
Compound 80r	

TABLE 11-continued

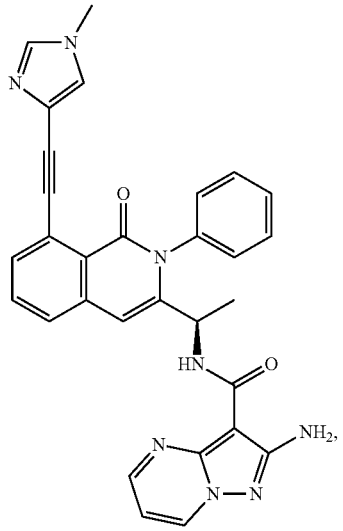
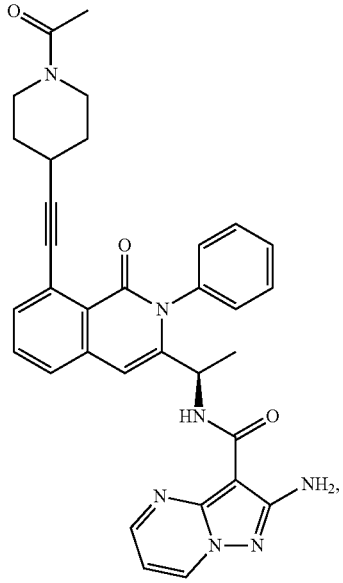
Compound 81r	
Compound 82r	

TABLE 11-continued

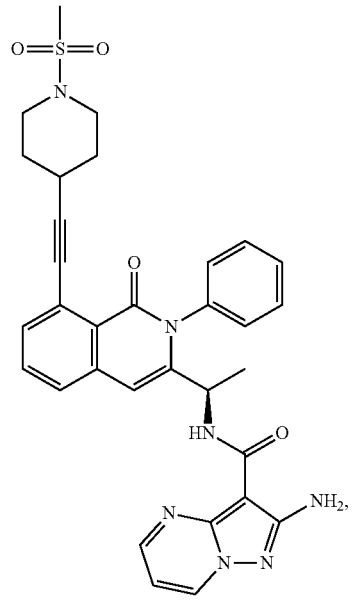
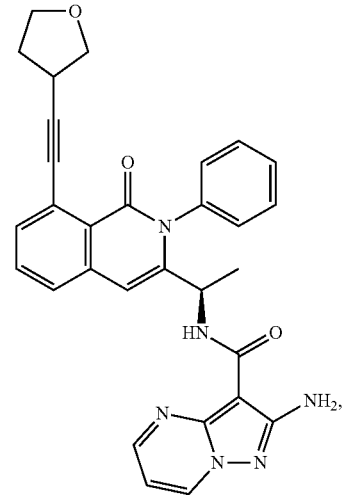
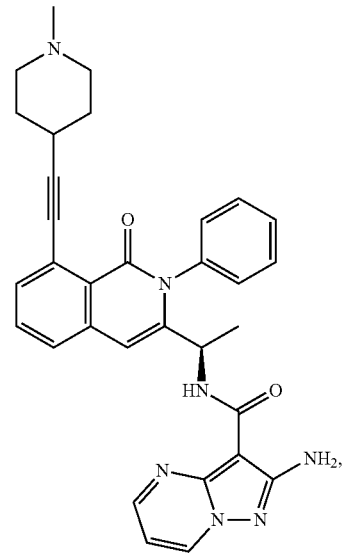
Compound 83r	
Compound 84r	
Compound 85r	

TABLE 11-continued

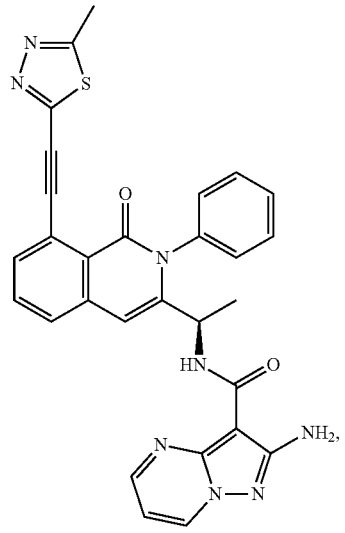
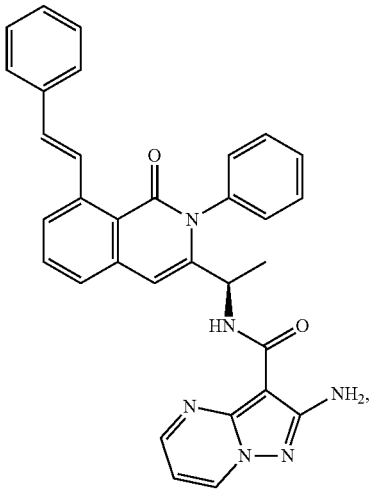
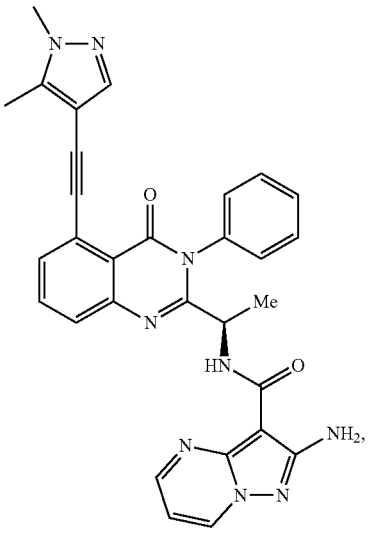
Compound 86r	
Compound 87r	
Compound 88r	

TABLE 11-continued

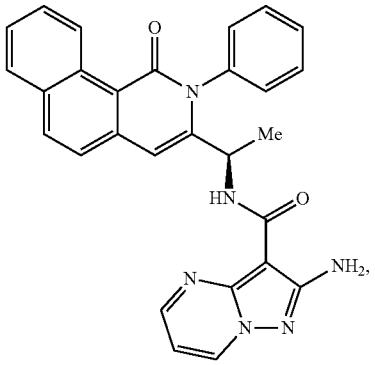
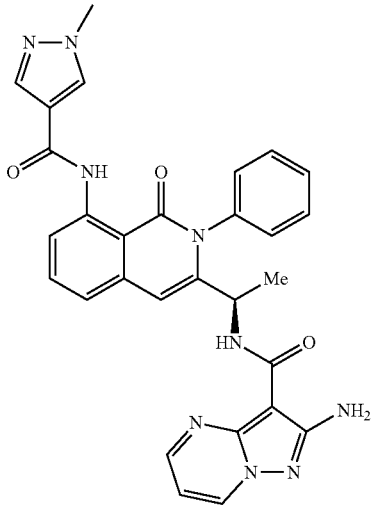
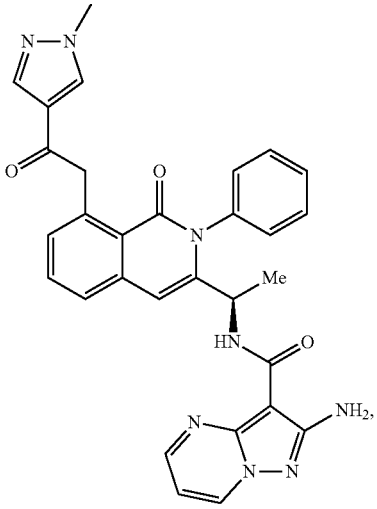
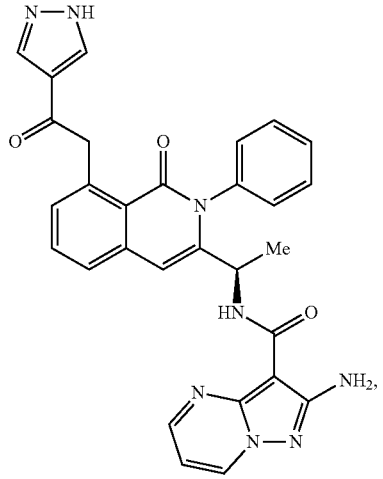
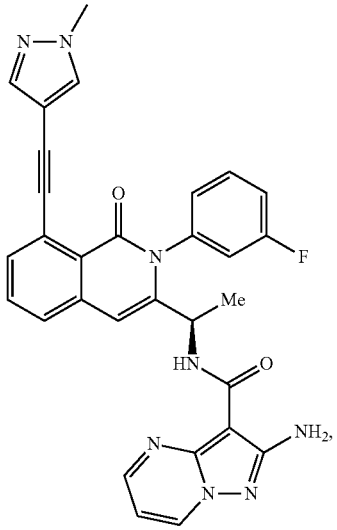
Compound 89r	
Compound 90r	
Compound 91r	

TABLE 11-continued

Compound 92r



Compound 93r



Compound 94r

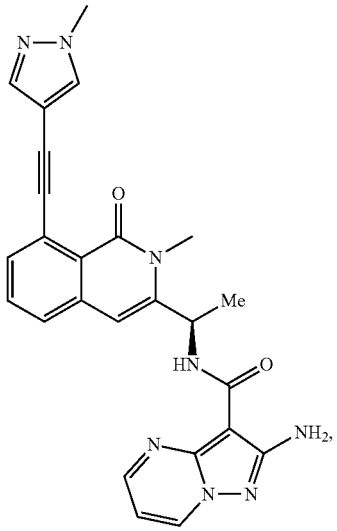
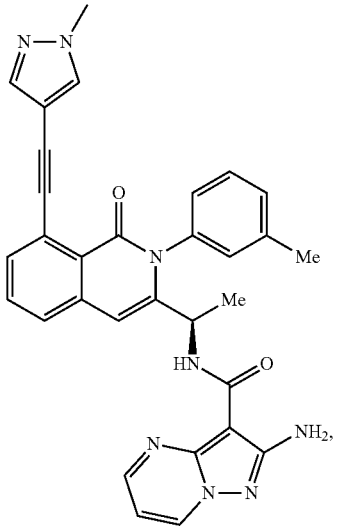
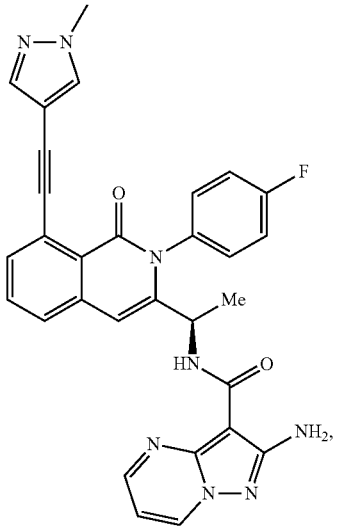


TABLE 11-continued

Compound 95r



Compound 96r



Compound 97r

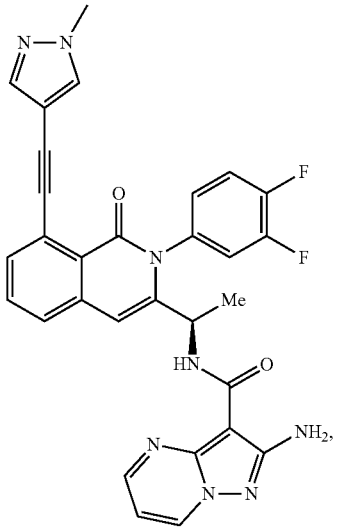


TABLE 11-continued

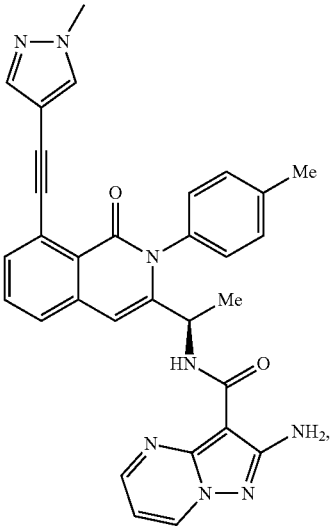
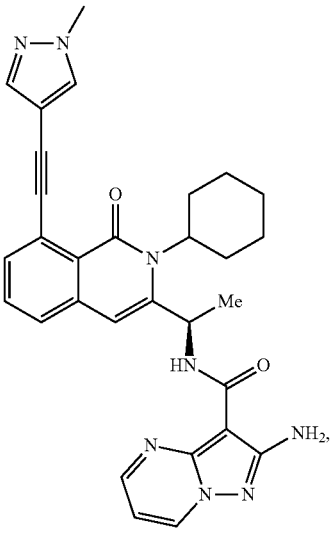
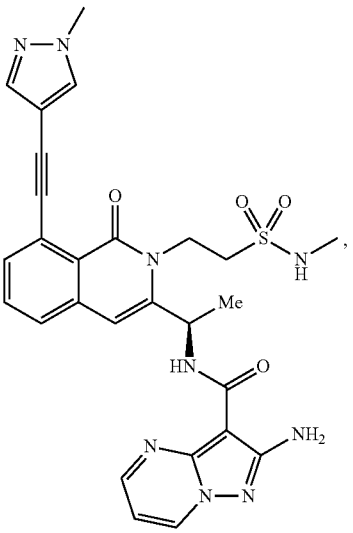
Compound 98r	
Compound 99r	
Compound 100r	

TABLE 11-continued

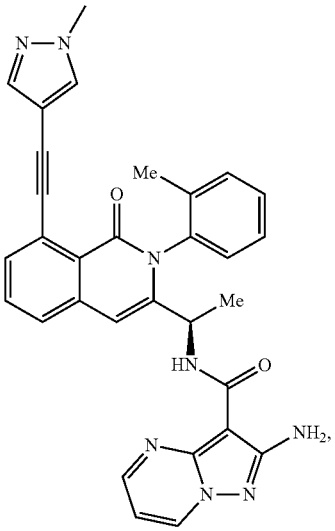
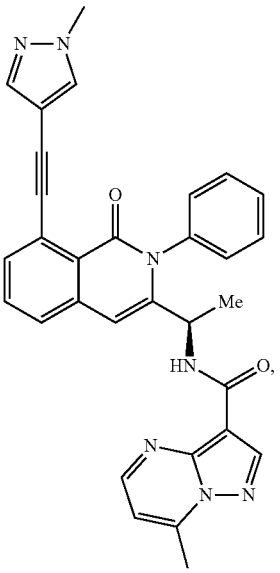
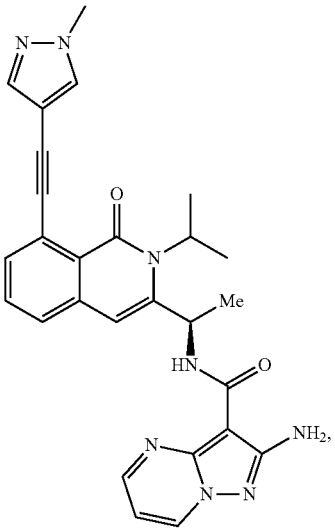
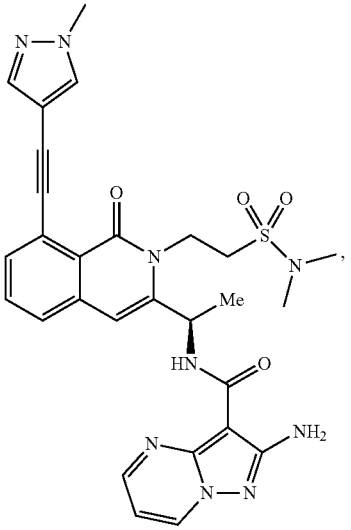
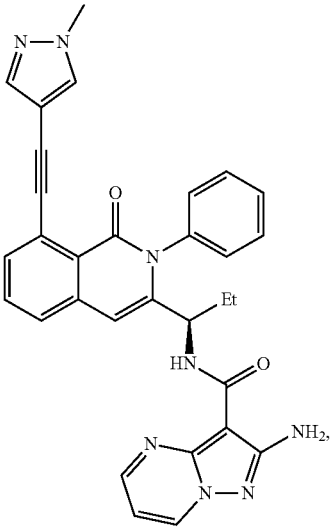
Compound 101r	
Compound 102r	
Compound 103r	

TABLE 11-continued

Compound 104r



Compound 105r



Compound 106r

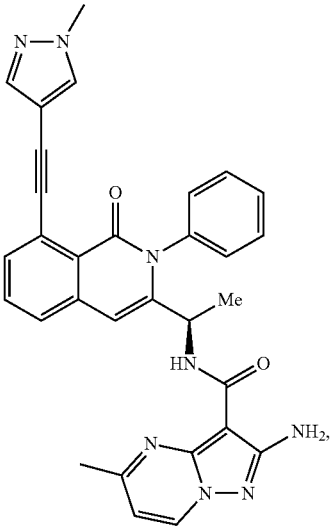
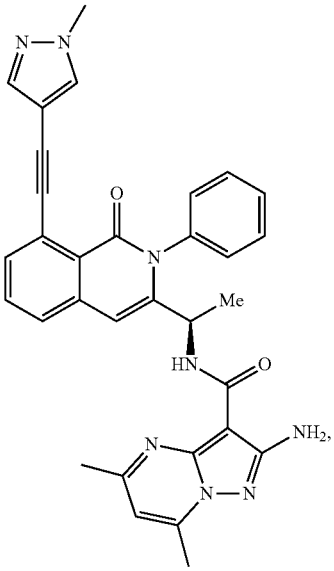


TABLE 11-continued

Compound 108r



Compound 109r

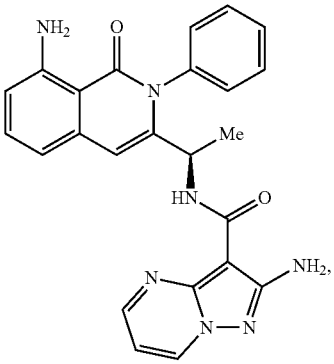


TABLE 12

Compound 1001r

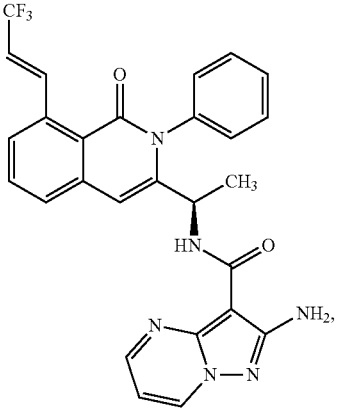


TABLE 12-continued

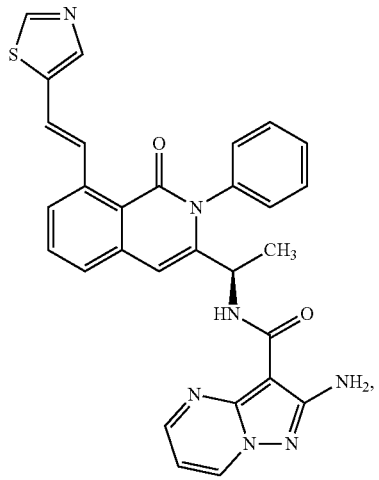
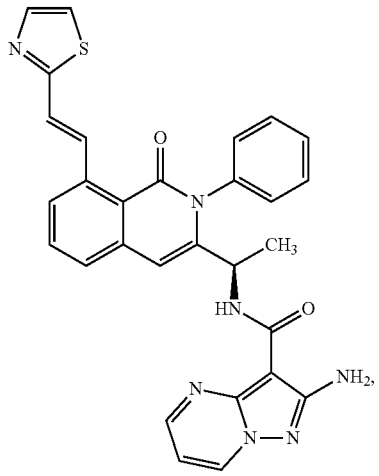
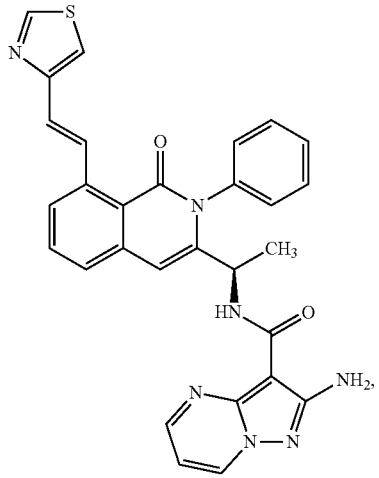
Compound 1002r	
Compound 1003r	
Compound 1004r	

TABLE 12-continued

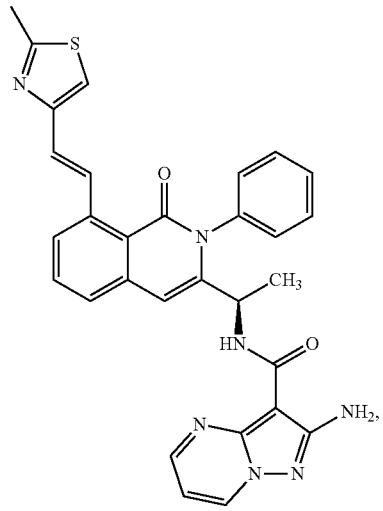
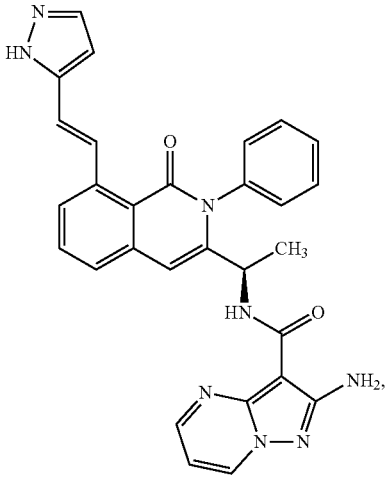
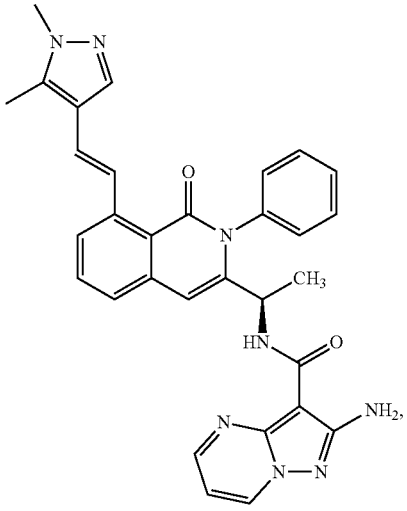
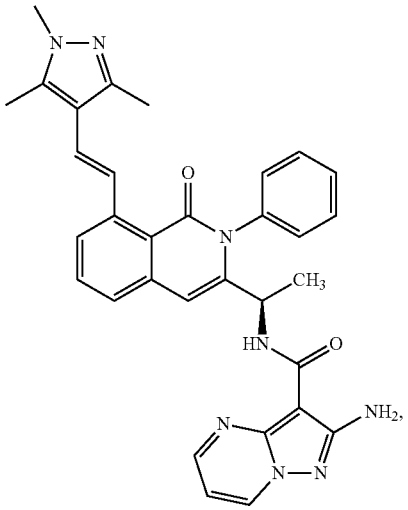
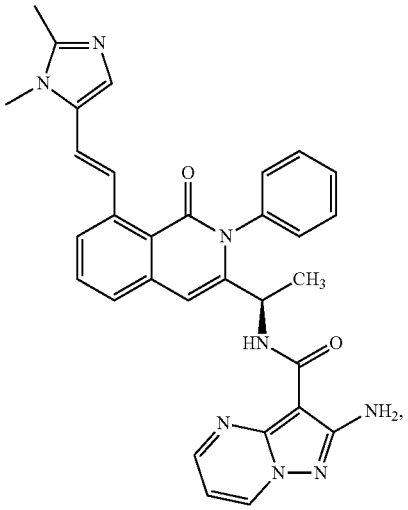
Compound 1005r	
Compound 1006r	
Compound 1007r	

TABLE 12-continued

Compound 1008r



Compound 1009r



Compound 1010r

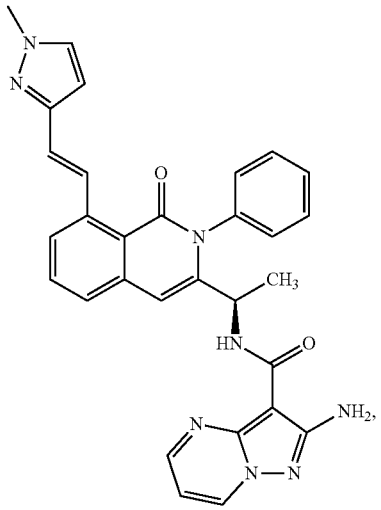
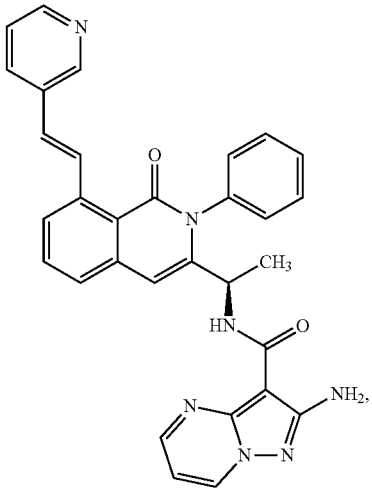
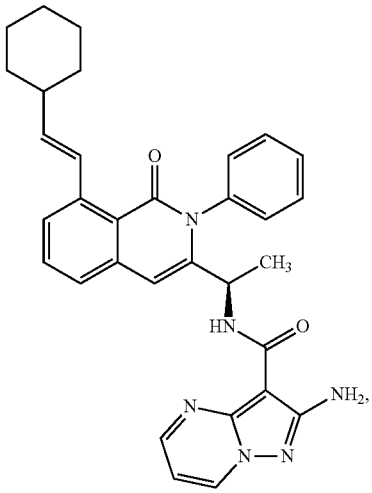


TABLE 12-continued

Compound 1011r



Compound 1012r



Compound 1013r

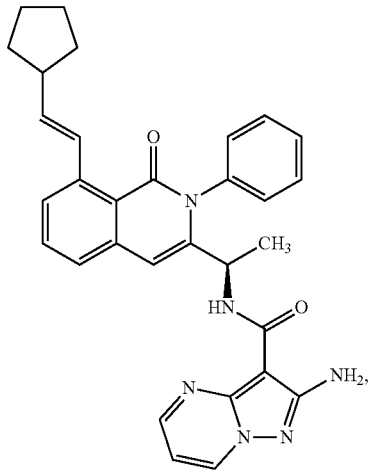


TABLE 12-continued

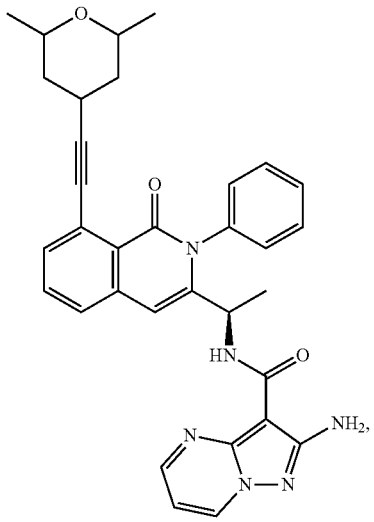
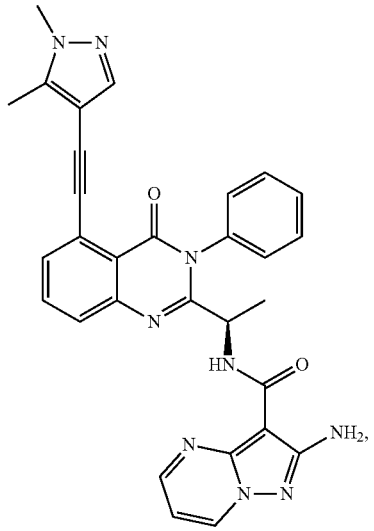
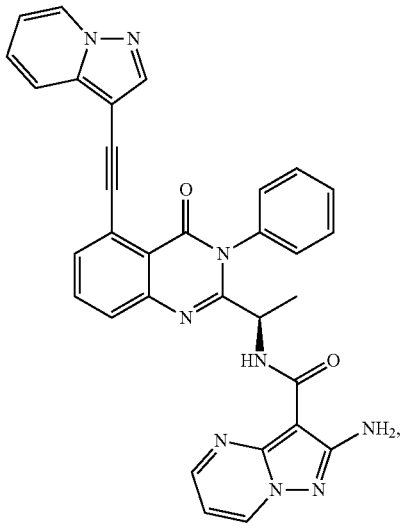
Compound 1014r	
Compound 1015r	
Compound 1016r	

TABLE 12-continued

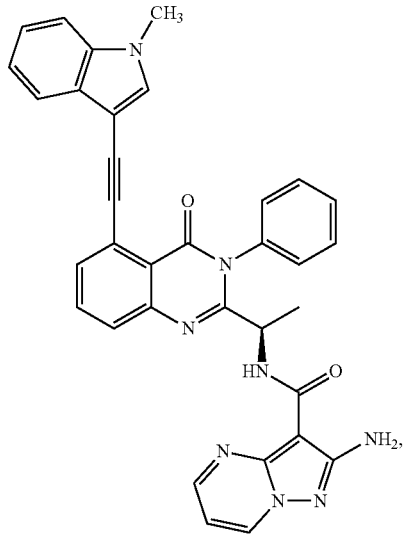
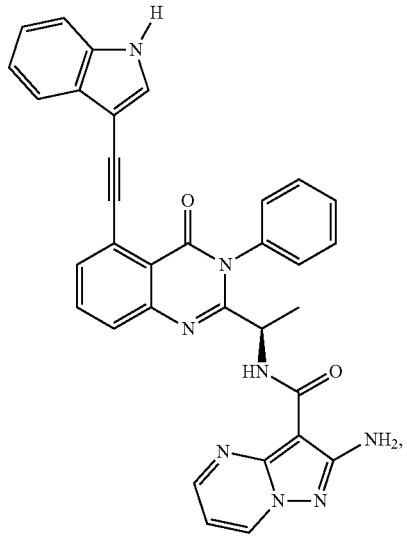
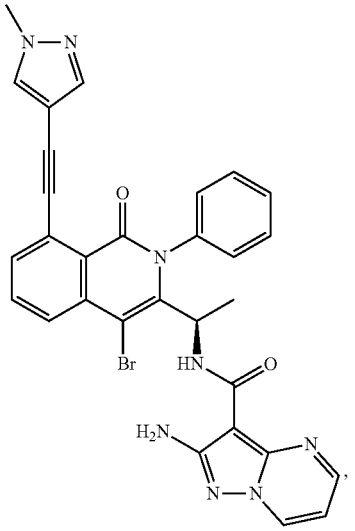
Compound 1017r	
Compound 1018r	
Compound 1041r	

TABLE 12-continued

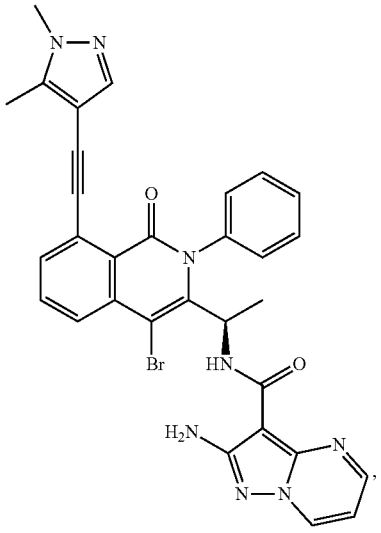
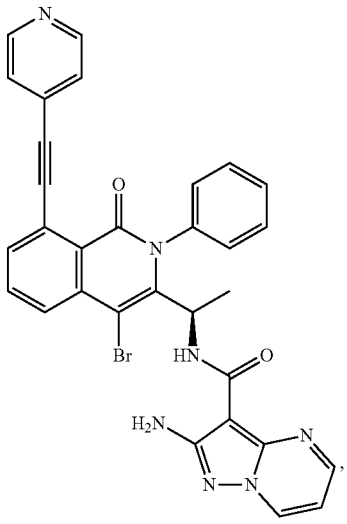
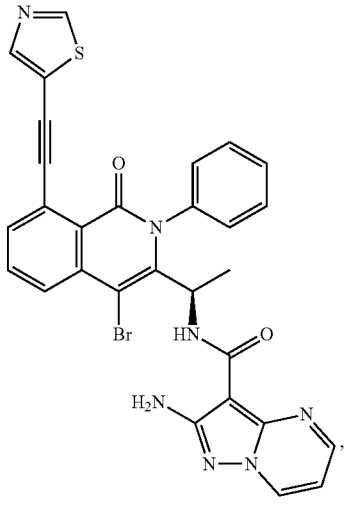
Compound 1042r	
Compound 1043r	
Compound 1044r	

TABLE 12-continued

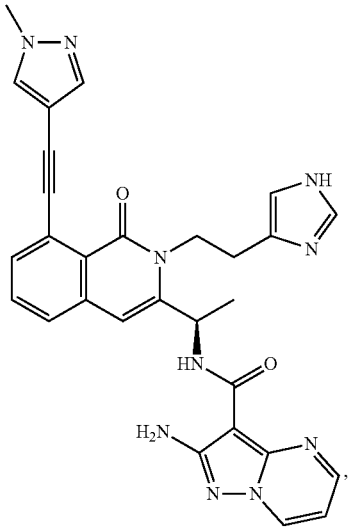
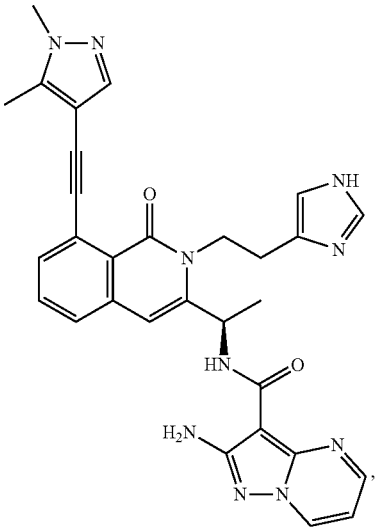
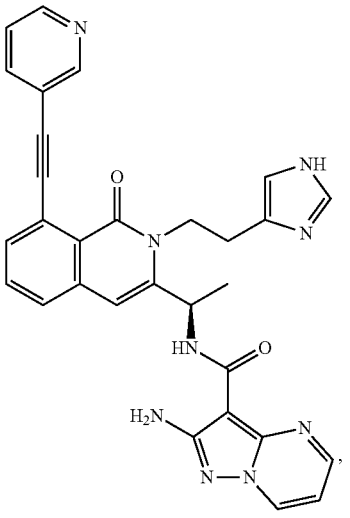
Compound 1045r	
Compound 1046r	
Compound 1047r	

TABLE 12-continued

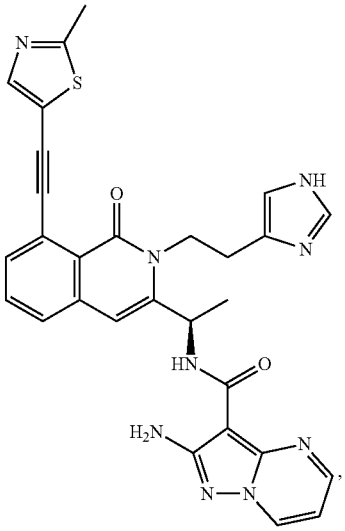
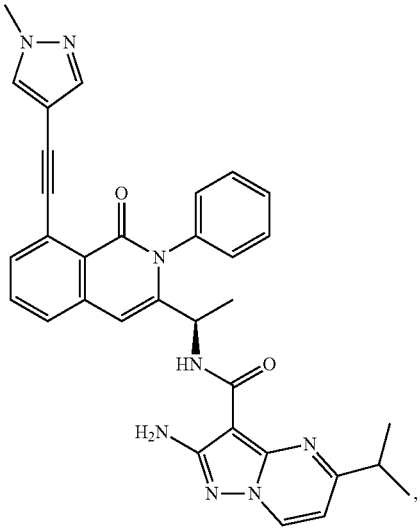
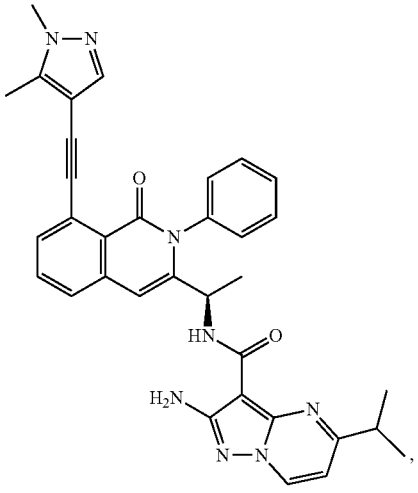
Compound 1048r	
Compound 1049r	
Compound 1050r	

TABLE 12-continued

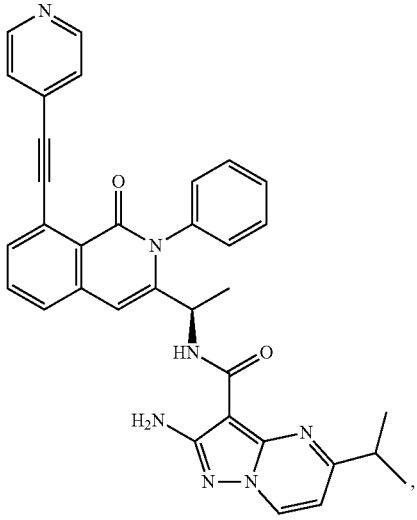
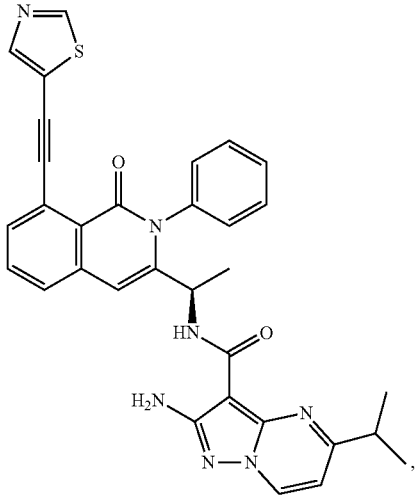
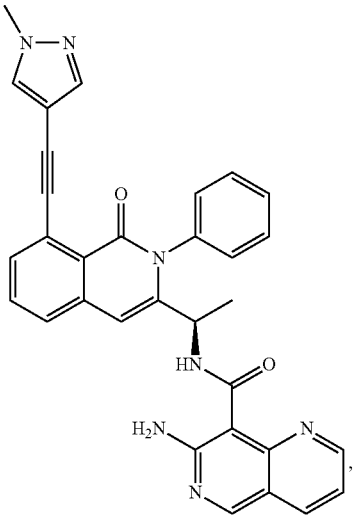
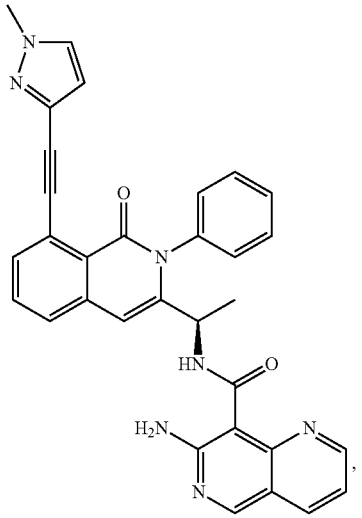
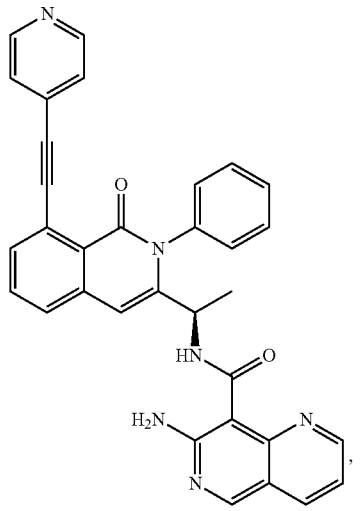
Compound 1051r	
Compound 1052r	
Compound 1053r	

TABLE 12-continued

Compound 1054r



Compound 1055r



Compound 1056r

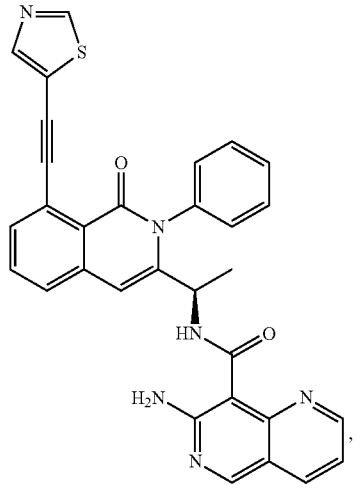
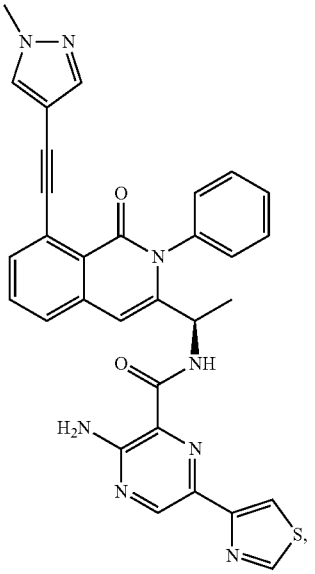


TABLE 12-continued

Compound 1057r



Compound 1058r

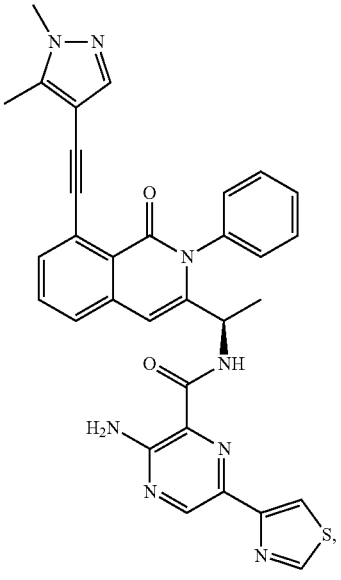
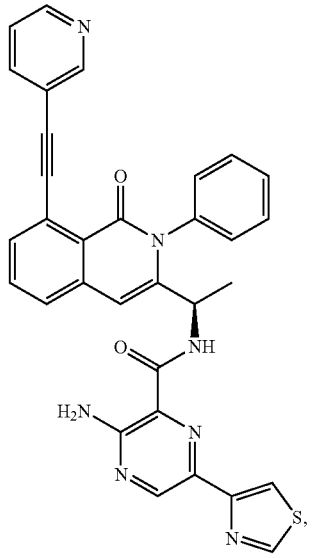
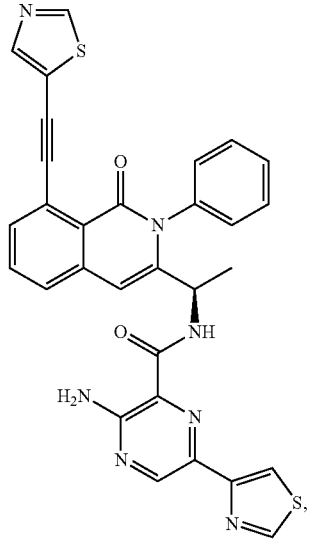


TABLE 12-continued

Compound 1059r



Compound 1060r



Compound 1061r

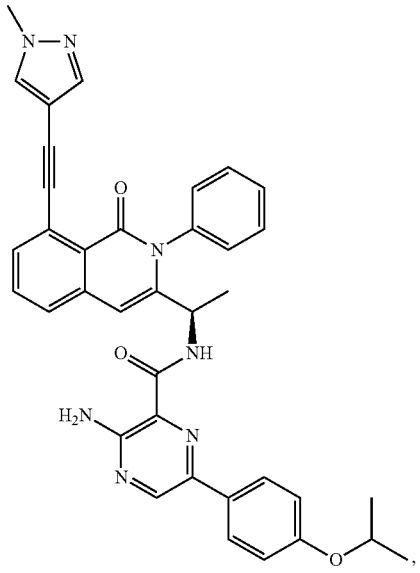
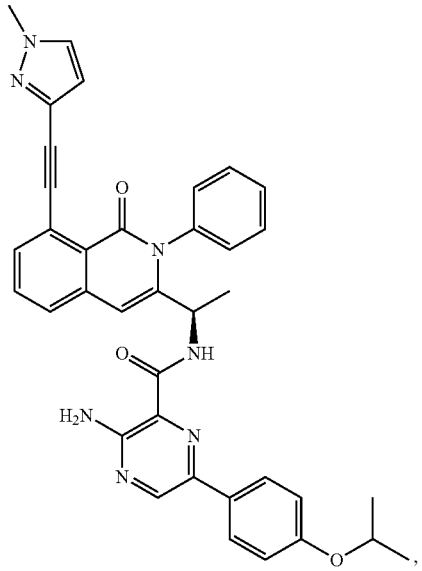


TABLE 12-continued

Compound 1062r



Compound 1063r

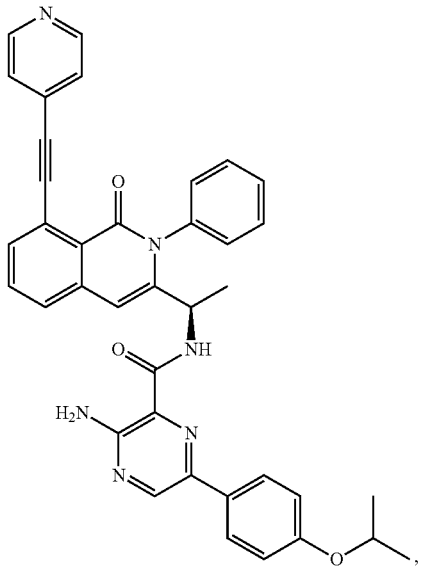


TABLE 12-continued

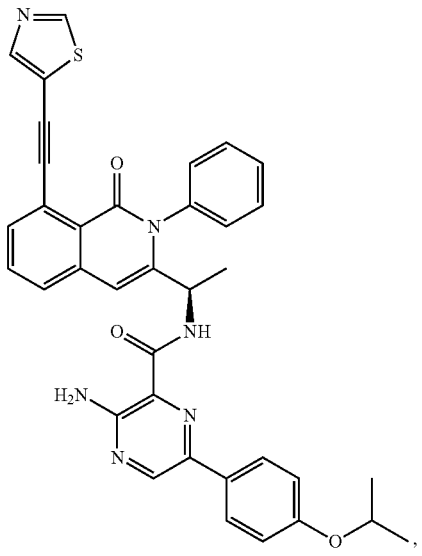
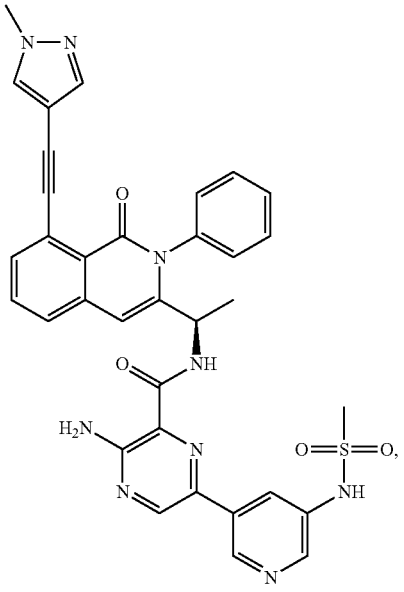
Compound 1064r	
Compound 1065r	

TABLE 12-continued

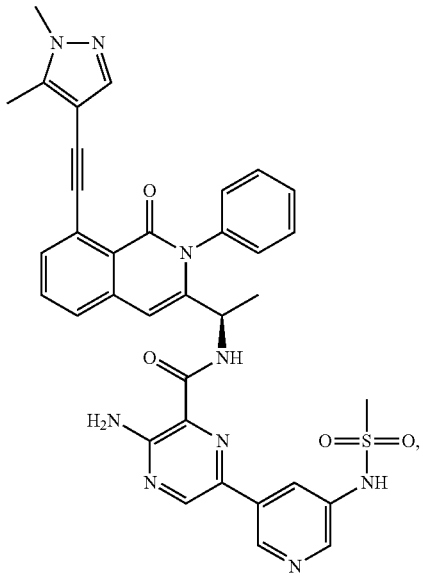
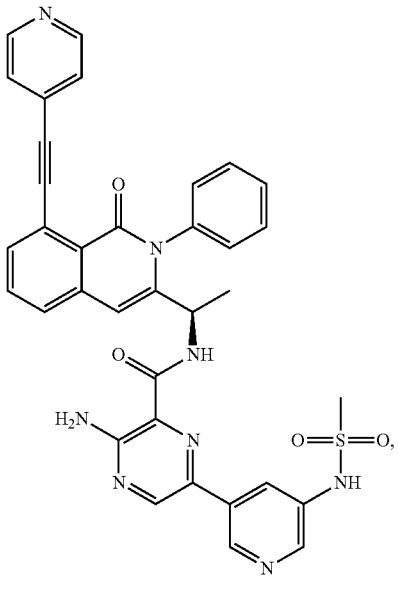
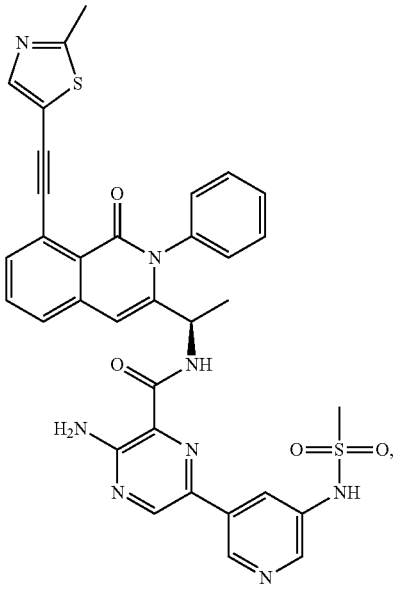
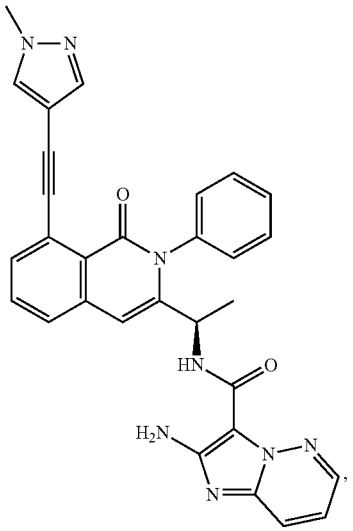
Compound 1066r	
Compound 1067r	

TABLE 12-continued

Compound 1068r



Compound 1069r



Compound 1070r

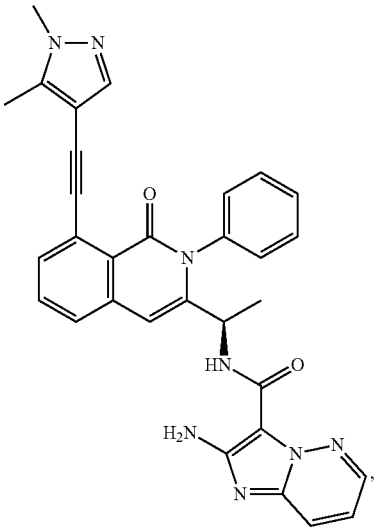
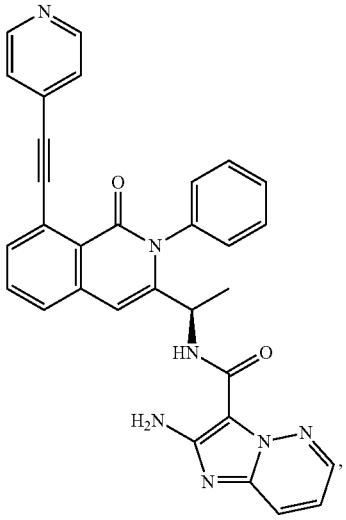
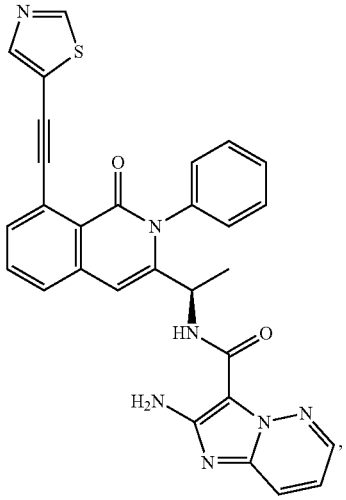


TABLE 12-continued

Compound 1071r



Compound 1072r



Compound 1073r

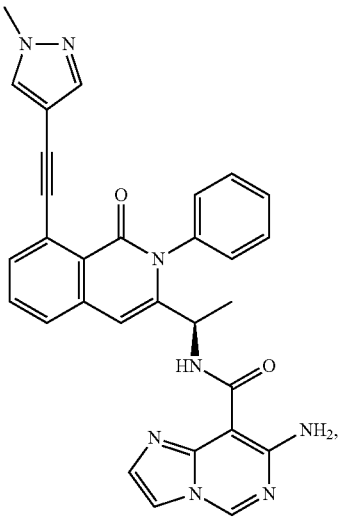


TABLE 12-continued

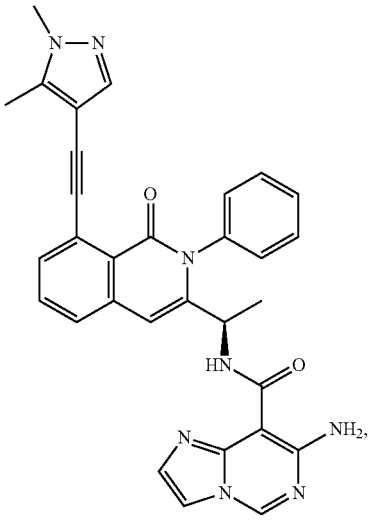
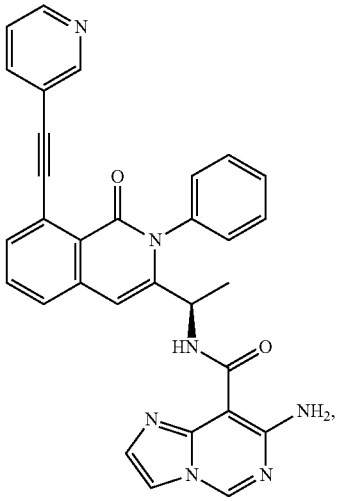
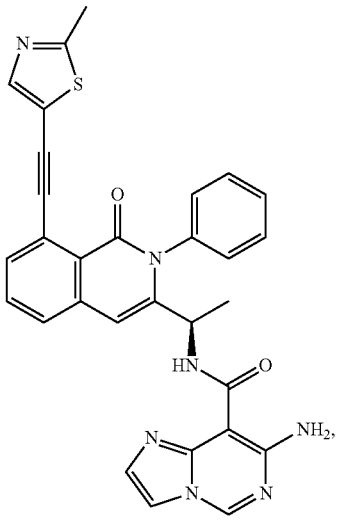
Compound 1074r	
Compound 1075r	
Compound 1076r	

TABLE 12-continued

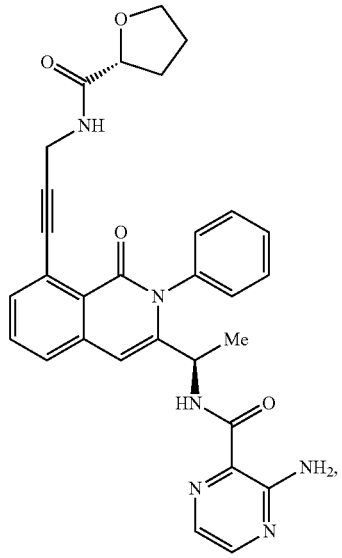
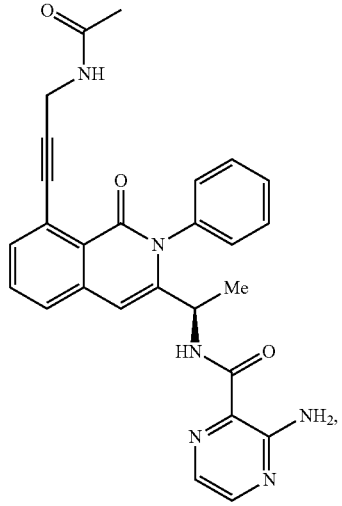
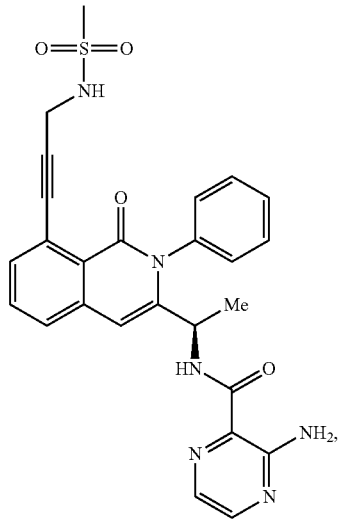
Compound 1077r	
Compound 1078r	
Compound 1079r	

TABLE 12-continued

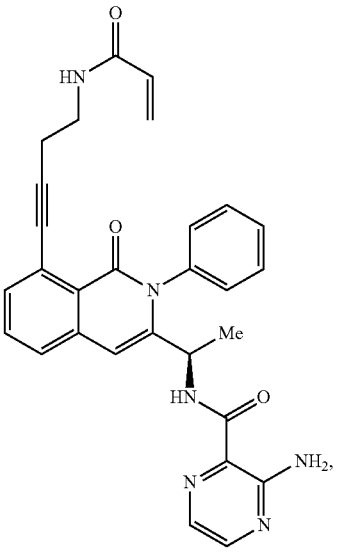
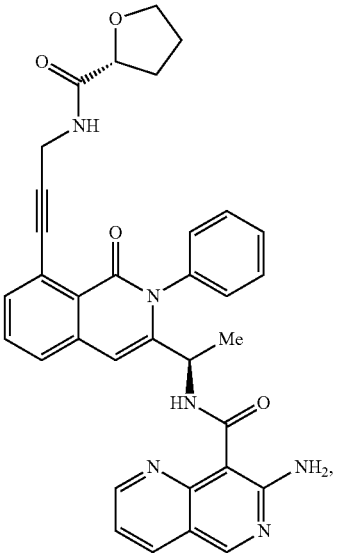
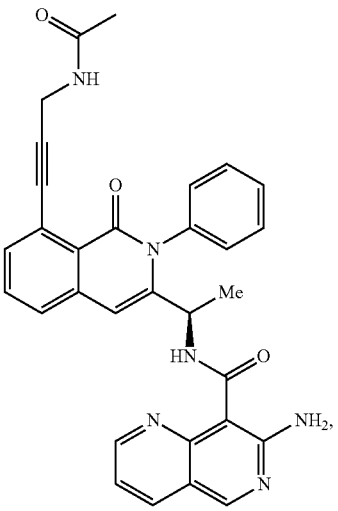
Compound 1080r	
Compound 1081r	
Compound 1082r	

TABLE 12-continued

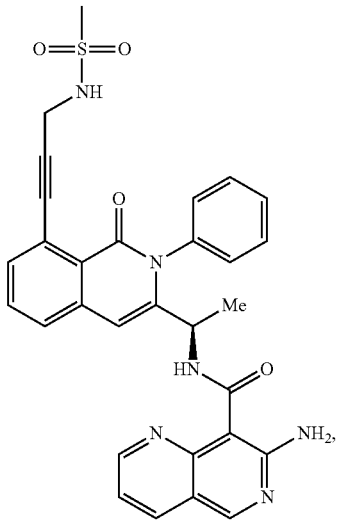
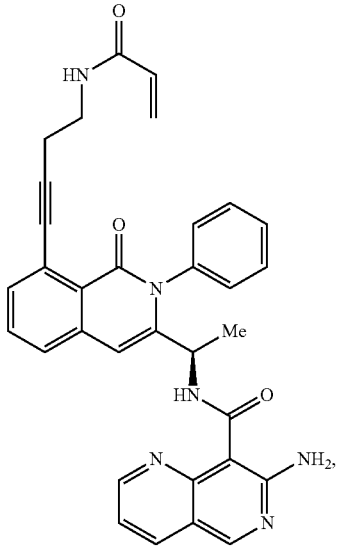
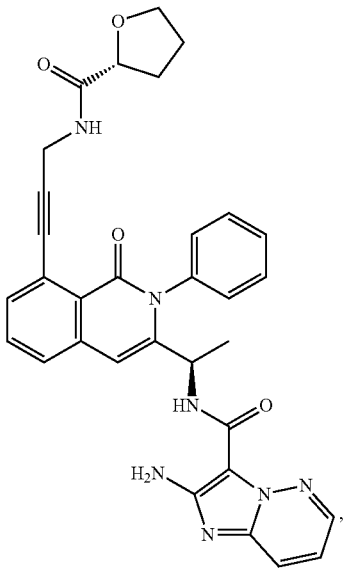
Compound 1083r	
Compound 1084r	
Compound 1085r	

TABLE 12-continued

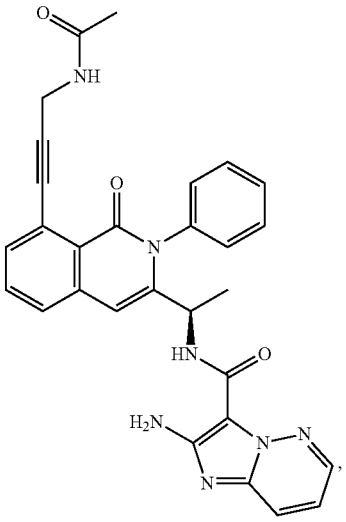
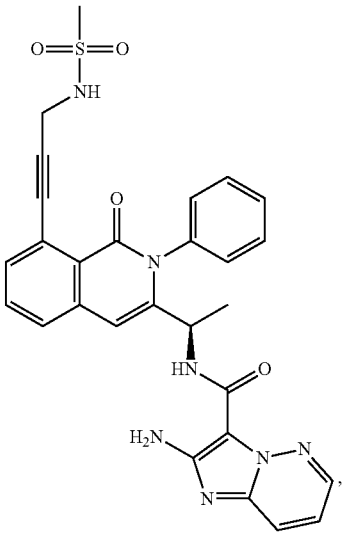
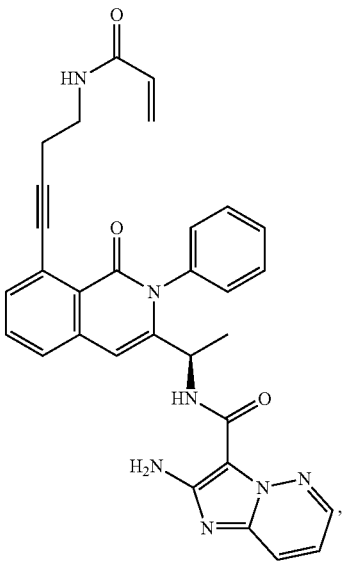
Compound 1086r	
Compound 1087r	
Compound 1088r	

TABLE 12-continued

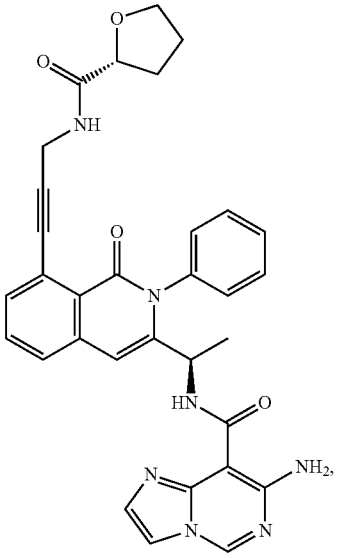
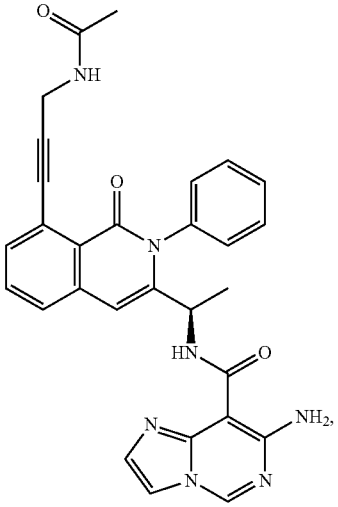
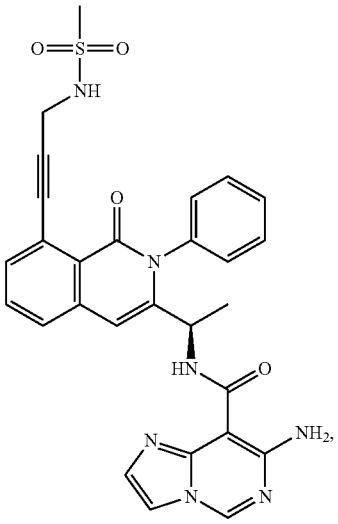
Compound 1089r	
Compound 1090r	
Compound 1091r	

TABLE 12-continued

Compound 1092r

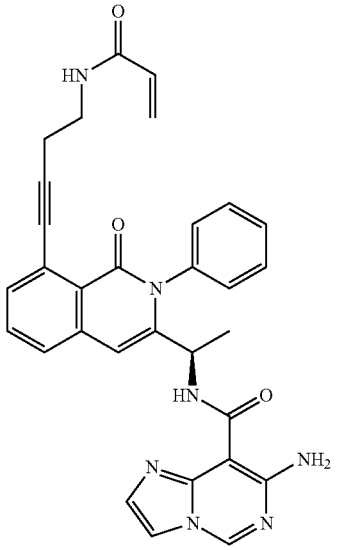
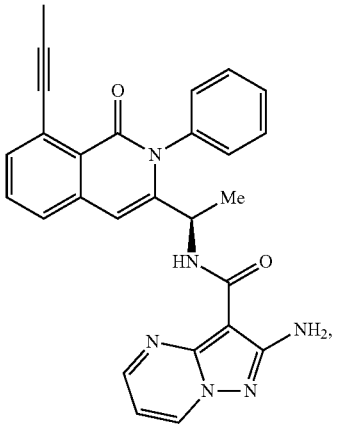


TABLE 13

Compound 2001r



Compound 2002r

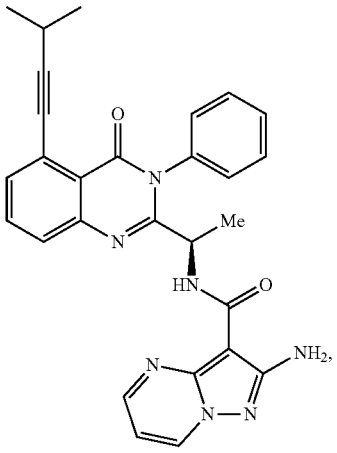
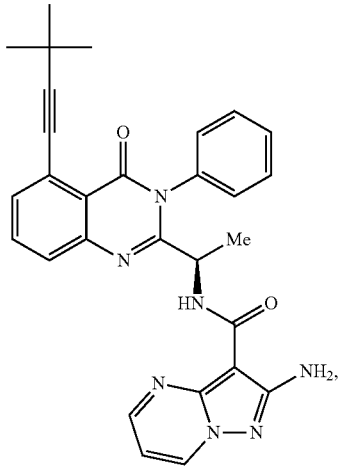
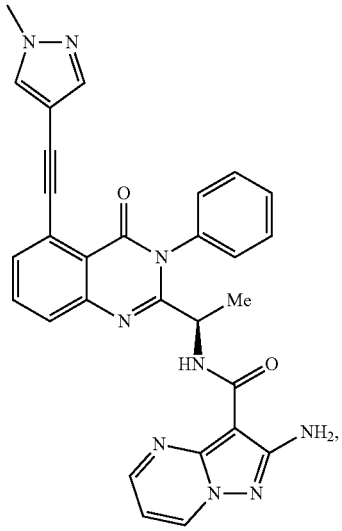


TABLE 13-continued

Compound 2003r



Compound 2004r



Compound 2005r

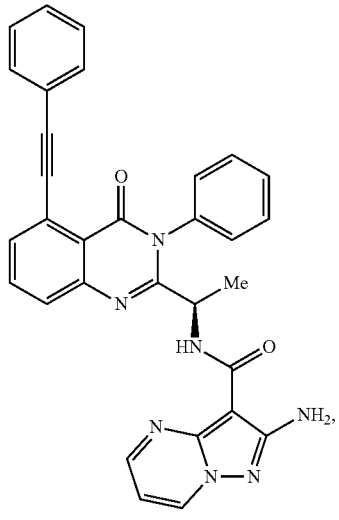


TABLE 13-continued

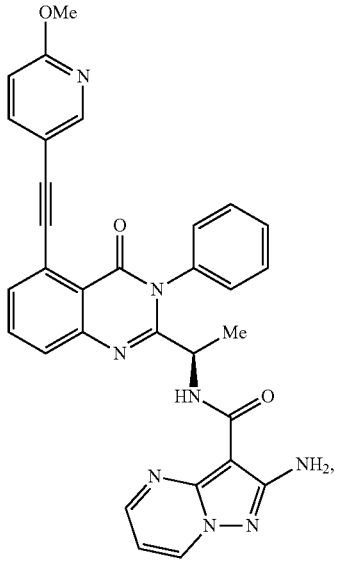
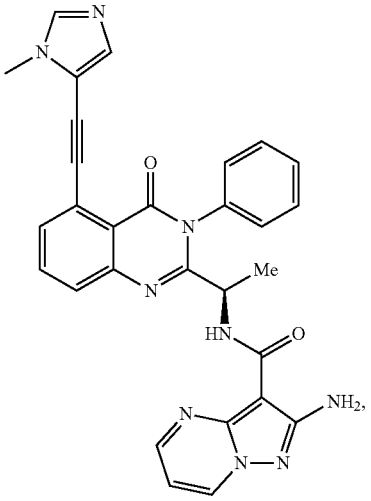
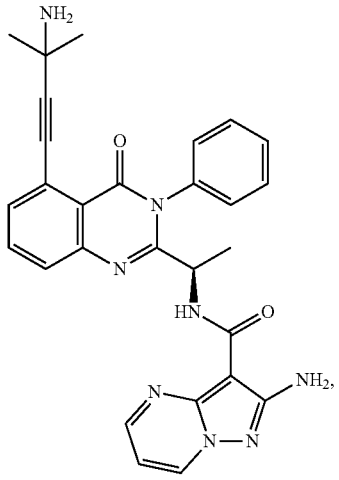
Compound 2006r	
Compound 2007r	
Compound 2008r	

TABLE 13-continued

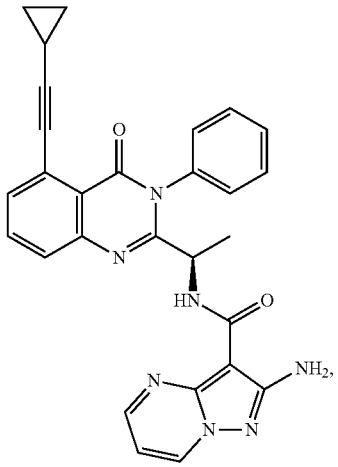
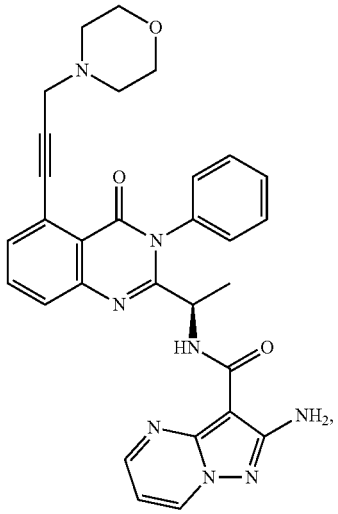
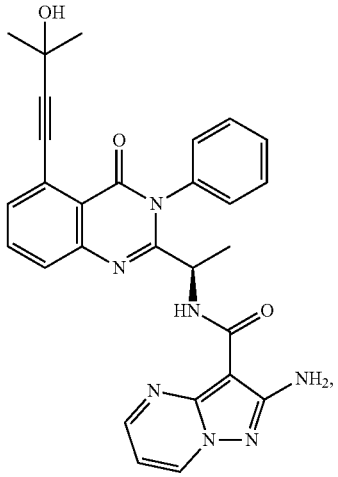
Compound 2009r	
Compound 2010r	
Compound 2011r	

TABLE 13-continued

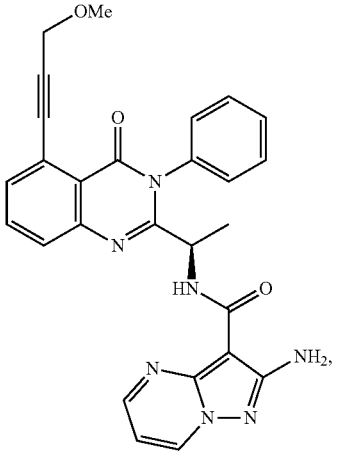
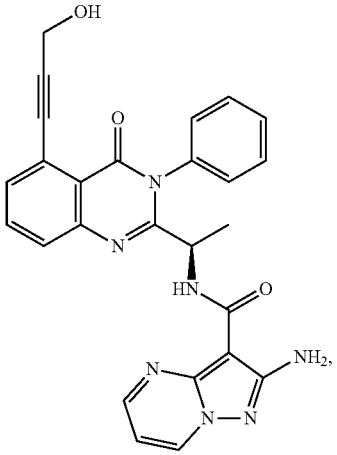
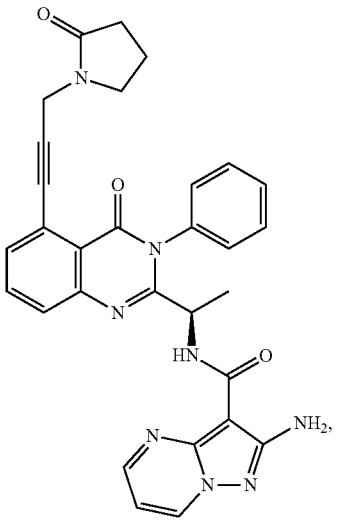
Compound 2012r	
Compound 2013r	
Compound 2014r	

TABLE 13-continued

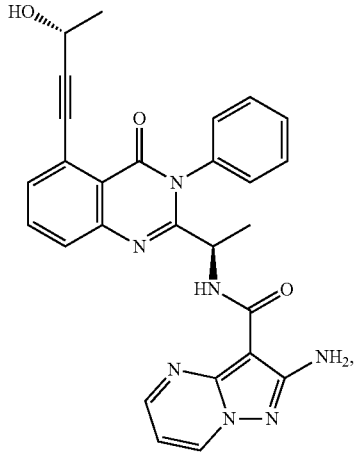
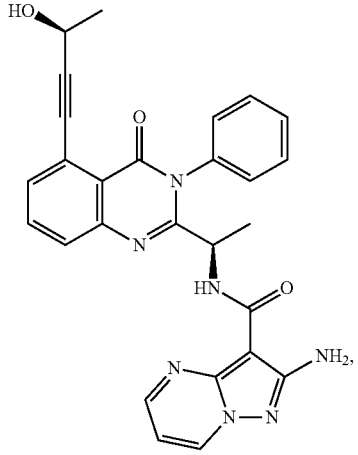
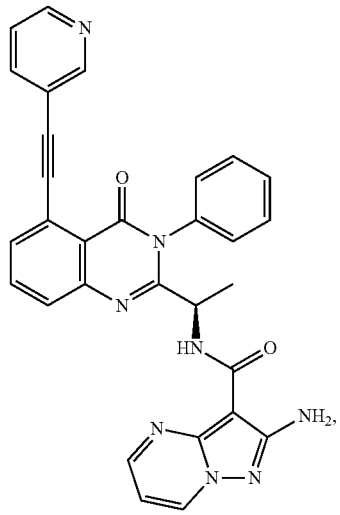
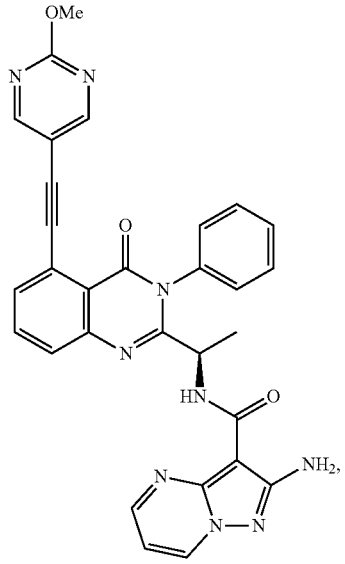
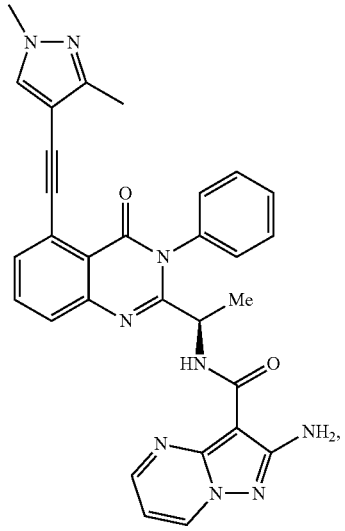
Compound 2015r	
Compound 2016r	
Compound 2017r	

TABLE 13-continued

Compound 2018r



Compound 2019r



Compound 2020r

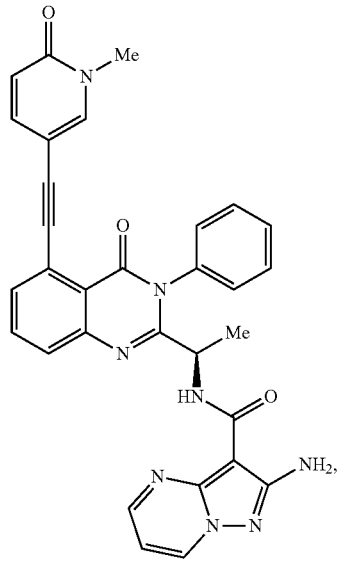
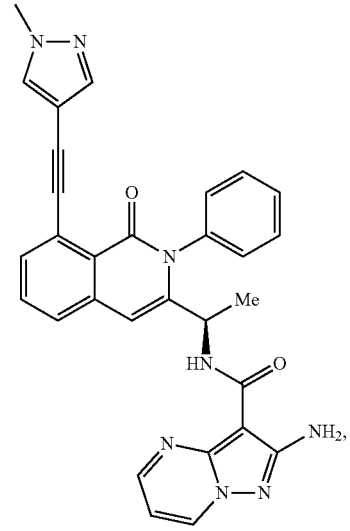
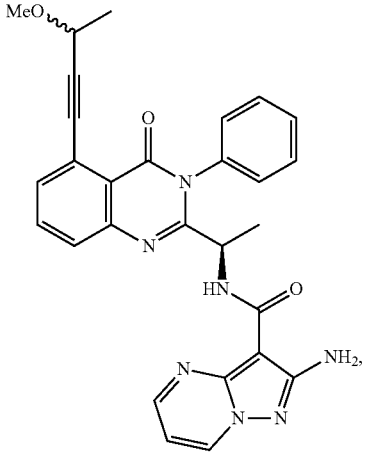


TABLE 13-continued

Compound 2021r



Compound 2022r



Compound 2023r

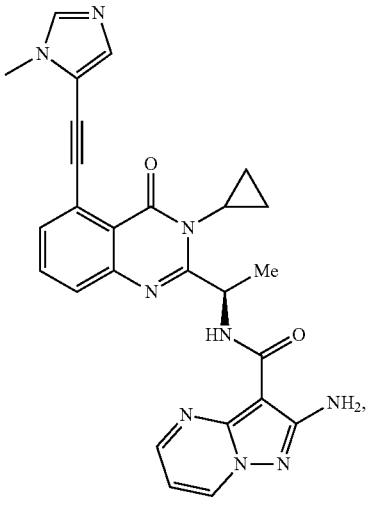
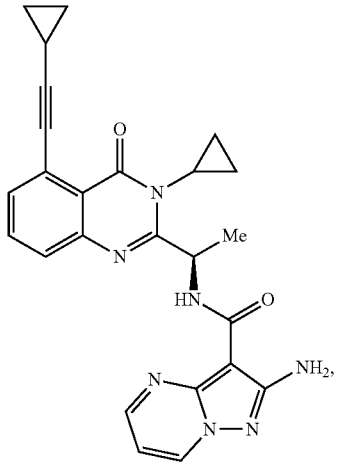
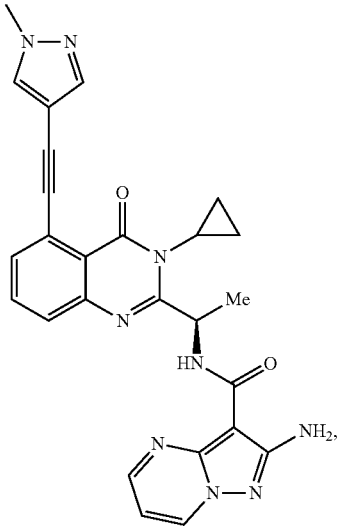


TABLE 13-continued

Compound 2024r



Compound 2025r



Compound 2026r

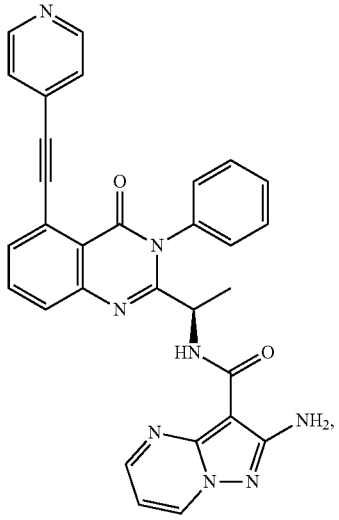
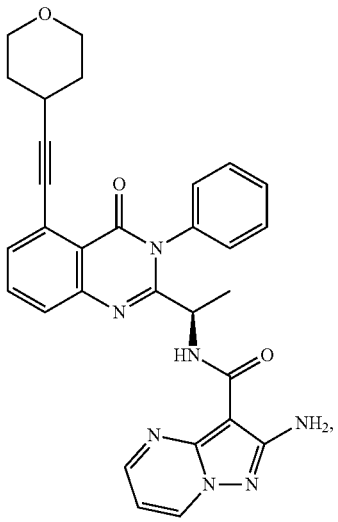
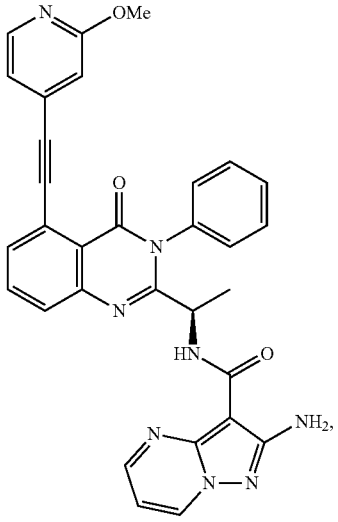


TABLE 13-continued

Compound 2027r



Compound 2028r



Compound 2029r

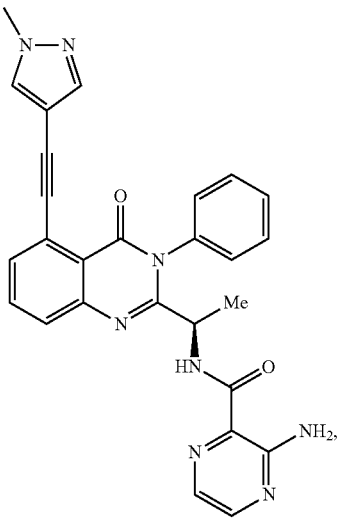


TABLE 13-continued

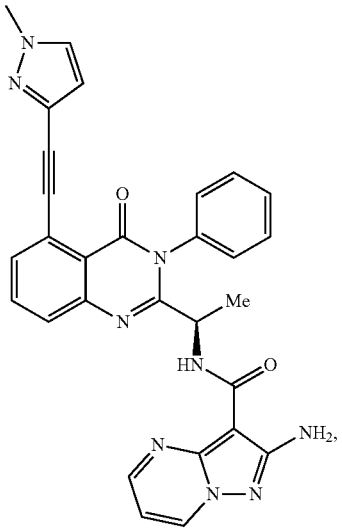
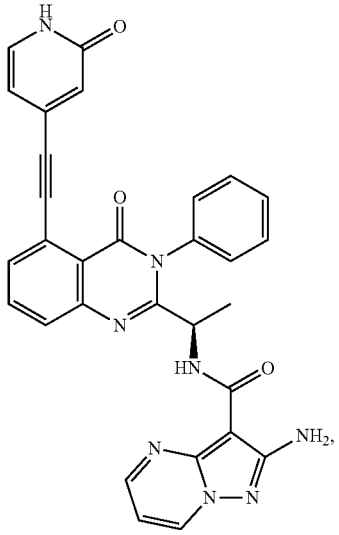
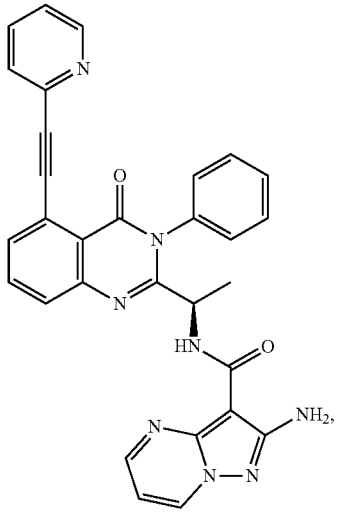
Compound 2030r	
Compound 2031r	
Compound 2032r	

TABLE 13-continued

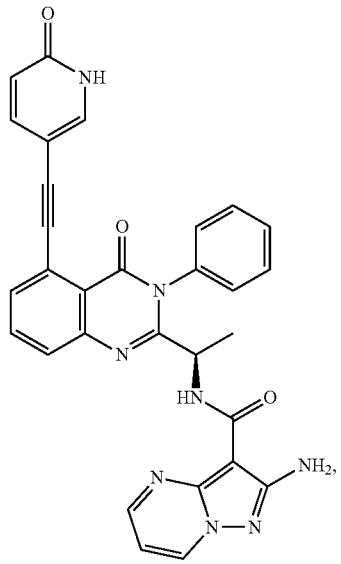
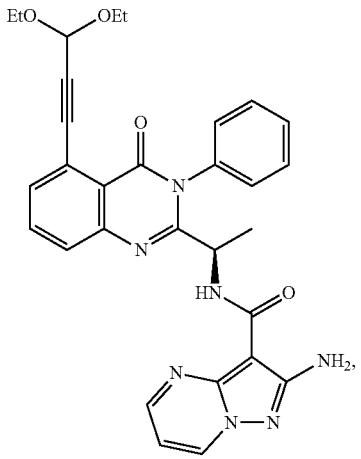
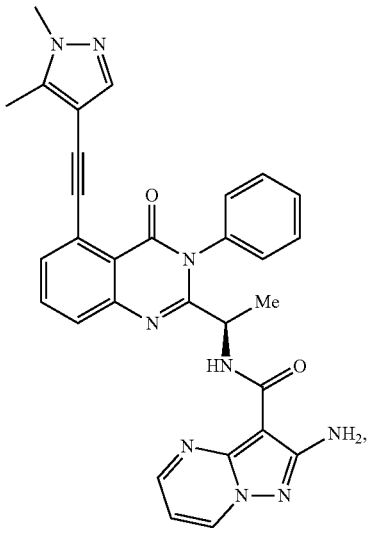
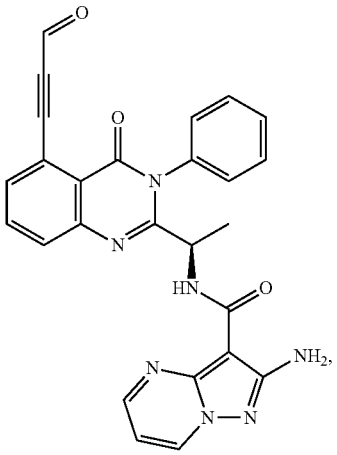
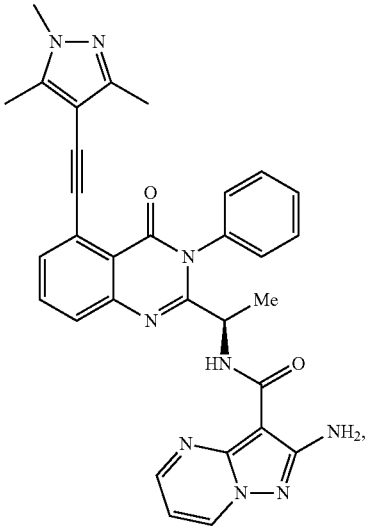
Compound 2033r	
Compound 2034r	
Compound 2035r	

TABLE 13-continued

Compound 2036r



Compound 2037r



Compound 2038r

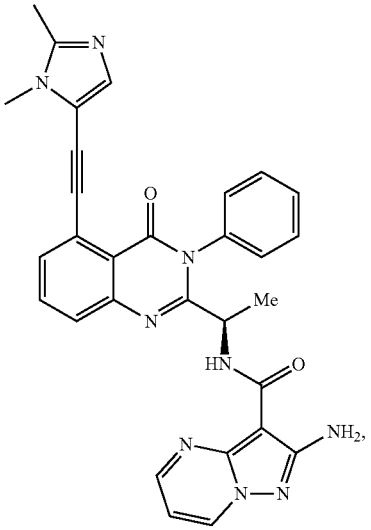
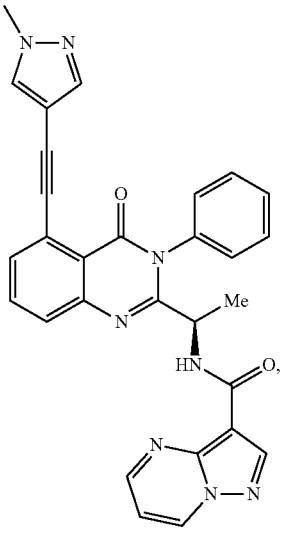
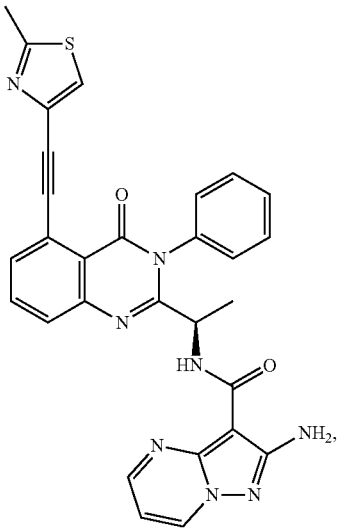


TABLE 13-continued

Compound 2039r



Compound 2040r



Compound 2041r

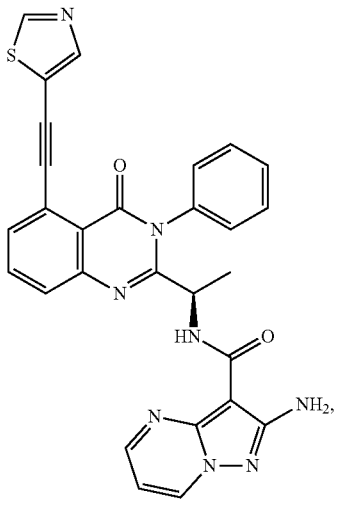


TABLE 13-continued

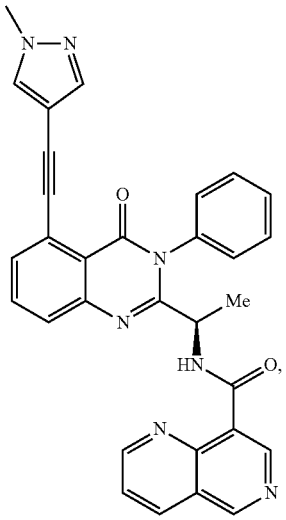
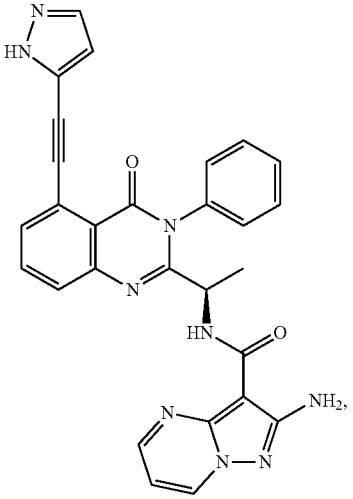
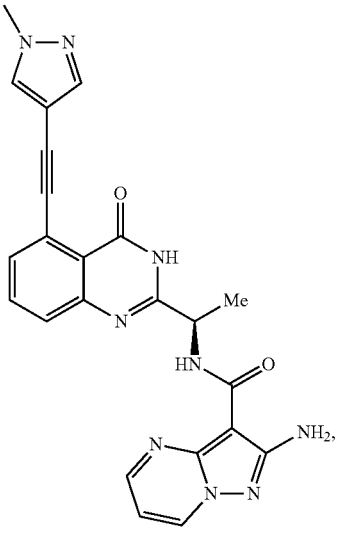
Compound 2042r	
Compound 2043r	
Compound 2044r	

TABLE 13-continued

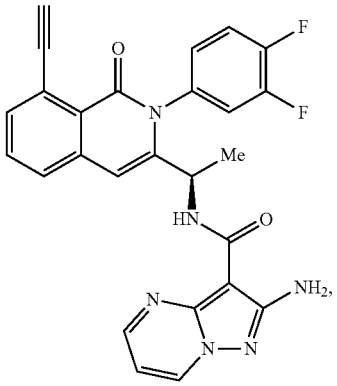
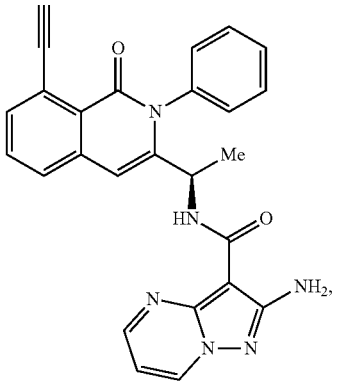
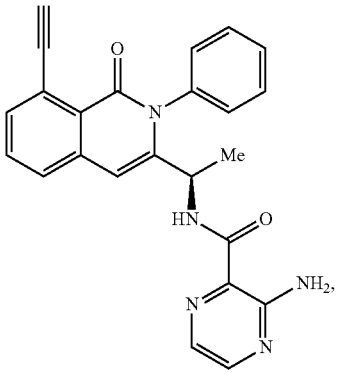
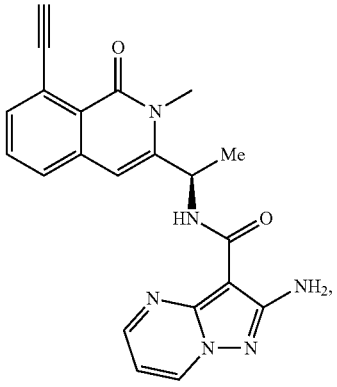
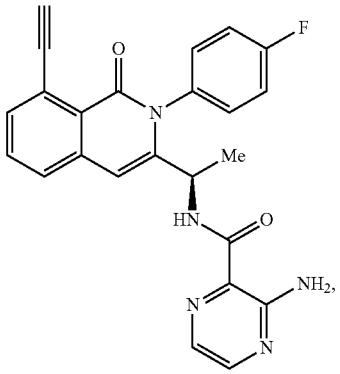
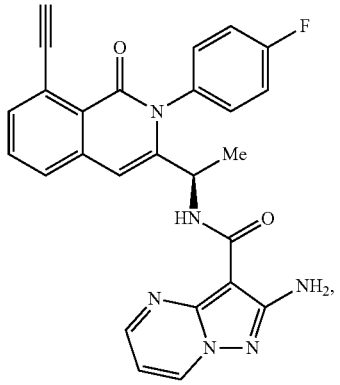
Compound 2045r	
Compound 2046r	
Compound 2047r	
Compound 2048r	

TABLE 13-continued

Compound 2049r



Compound 2050r



Compound 2051r

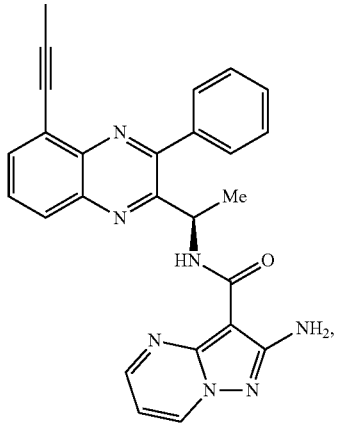
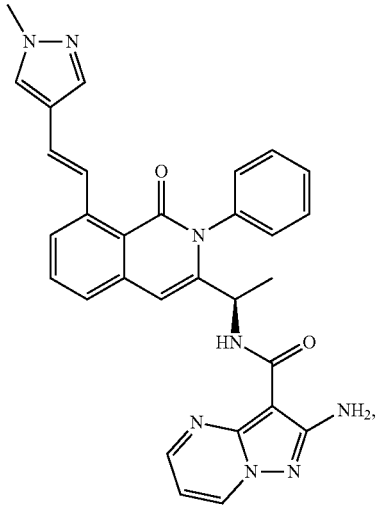
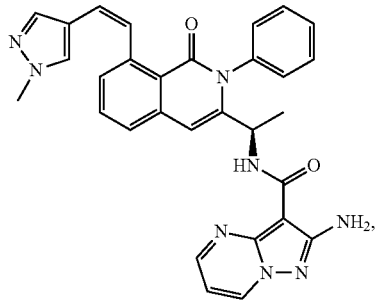


TABLE 13-continued

Compound 2052r



Compound 2053r



Compound 2054r

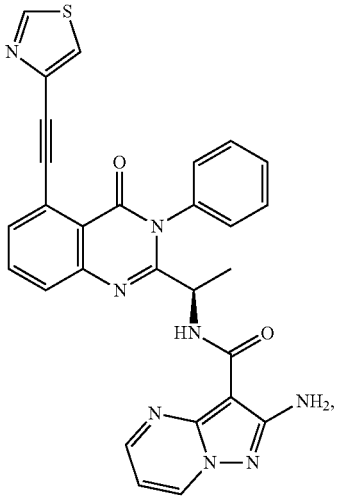


TABLE 13-continued

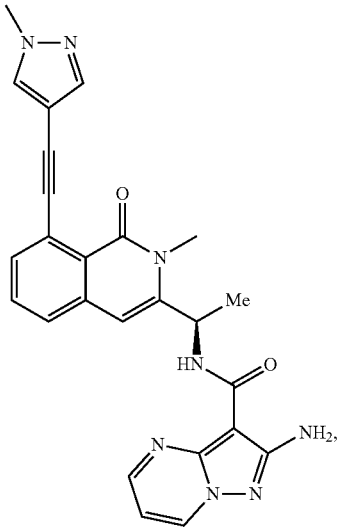
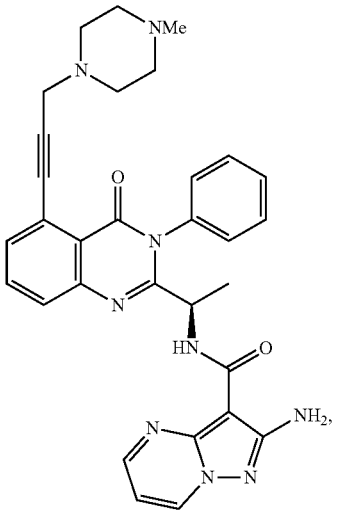
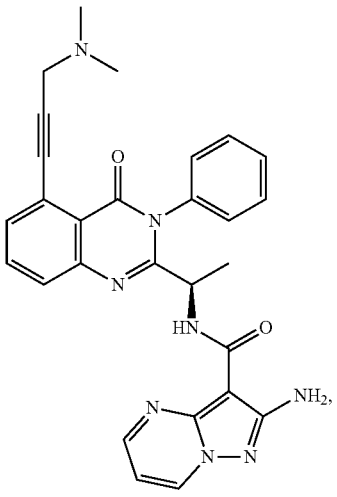
Compound 2055r	
Compound 2056r	
Compound 2057r	

TABLE 13-continued

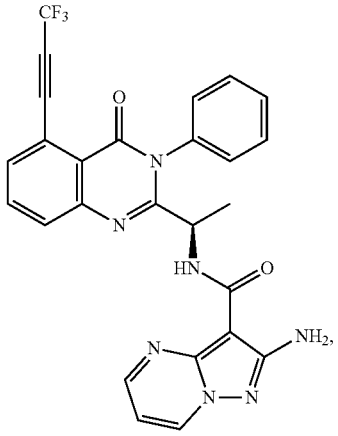
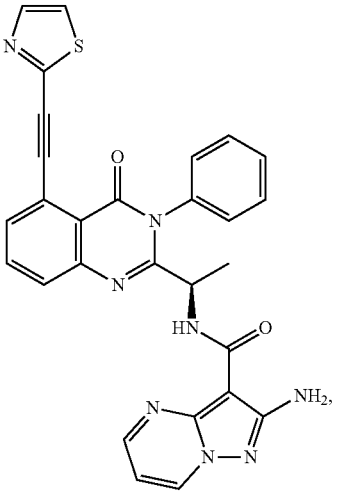
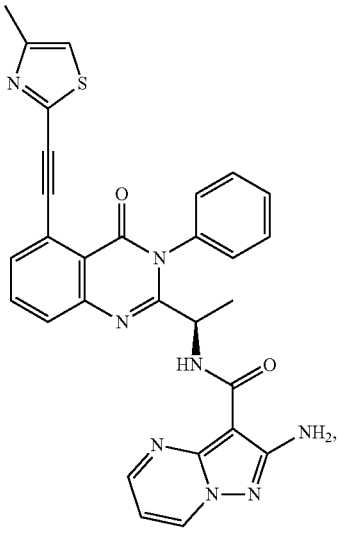
Compound 2058r	
Compound 2059r	
Compound 2060r	

TABLE 13-continued

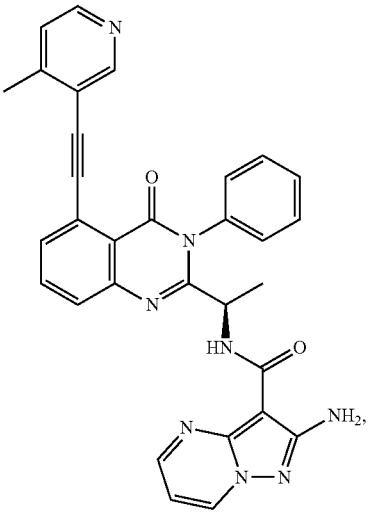
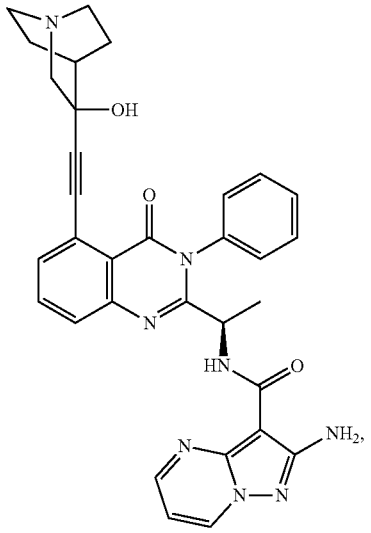
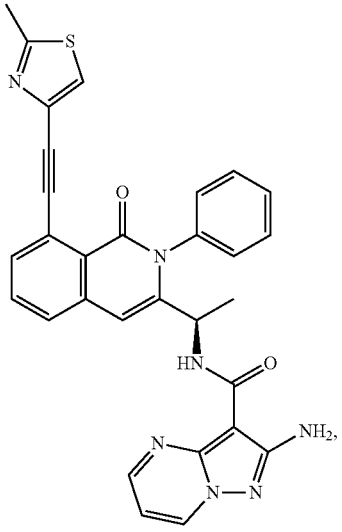
Compound 2061r	
Compound 2062r	
Compound 2063r	

TABLE 13-continued

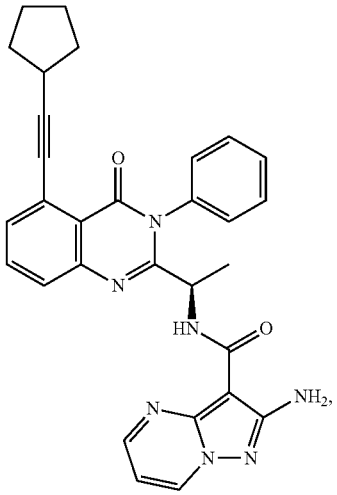
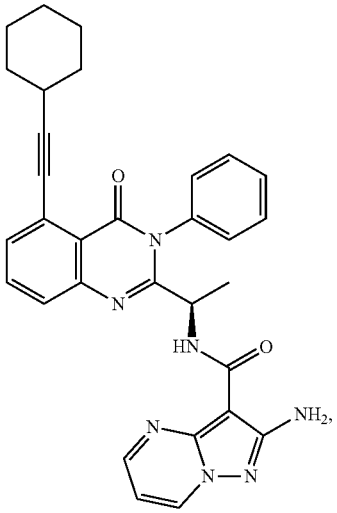
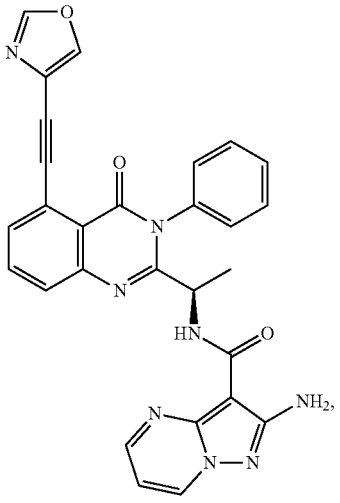
Compound 2064r	
Compound 2065r	
Compound 2066r	

TABLE 13-continued

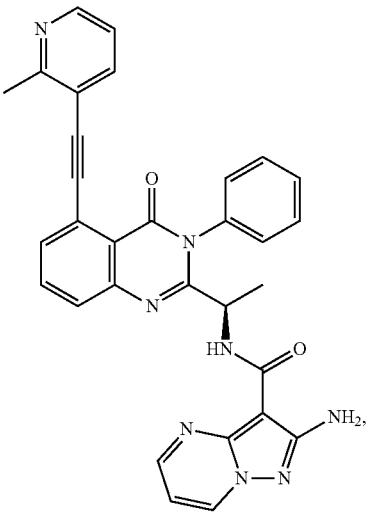
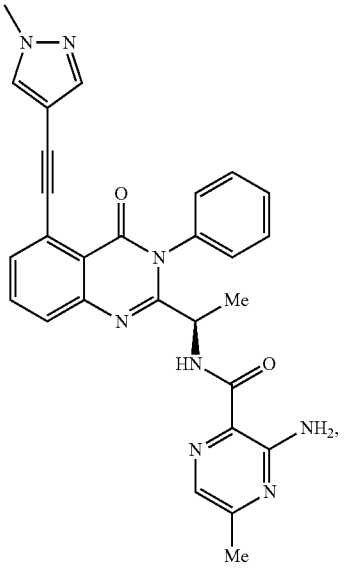
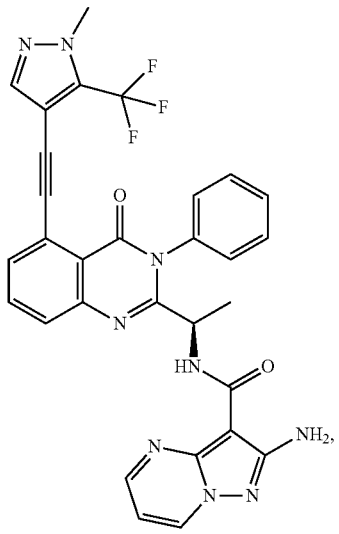
Compound 2067r	
Compound 2068r	
Compound 2069r	

TABLE 13-continued

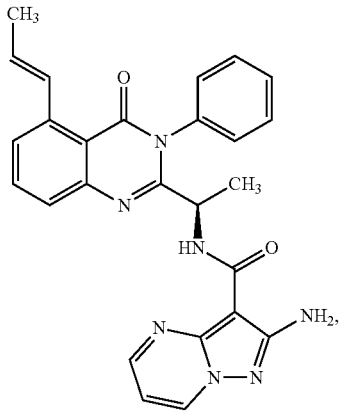
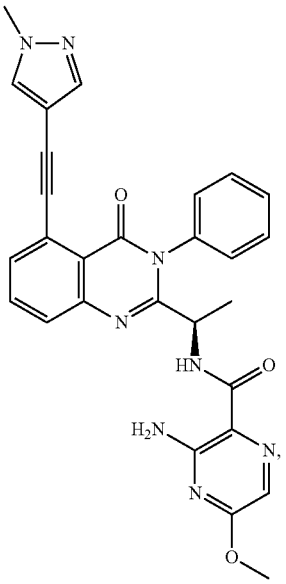
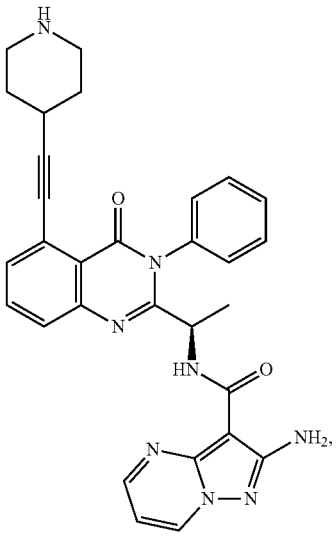
Compound 2070r	
Compound 2071r	
Compound 2072r	

TABLE 13-continued

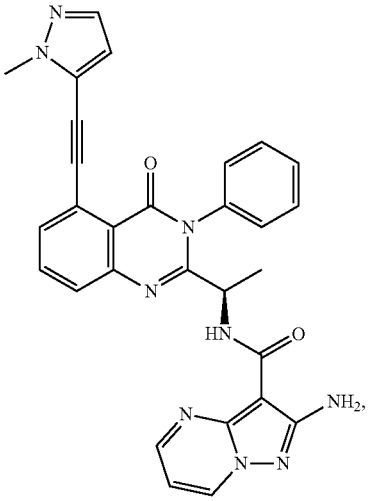
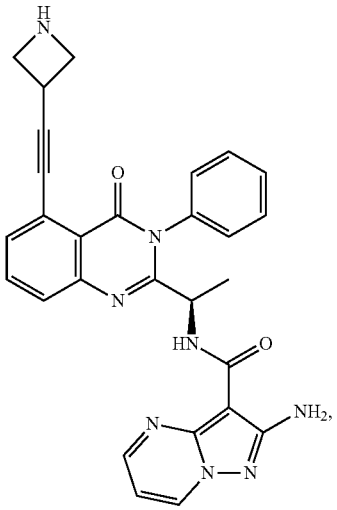
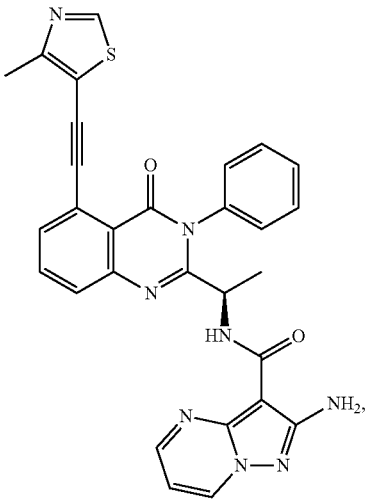
Compound 2073r	
Compound 2074r	
Compound 2075r	

TABLE 13-continued

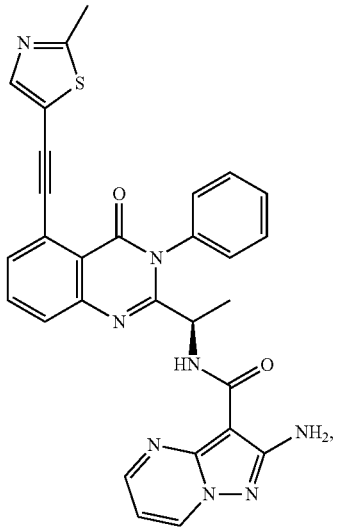
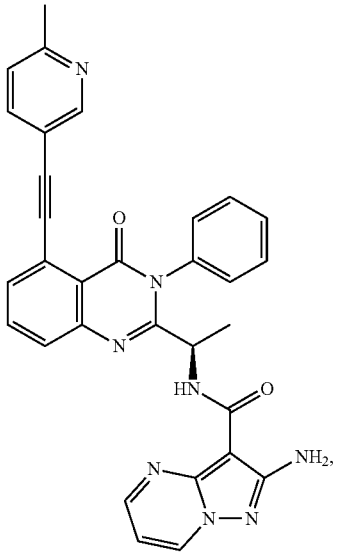
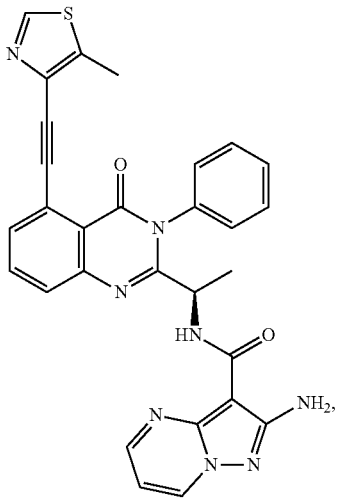
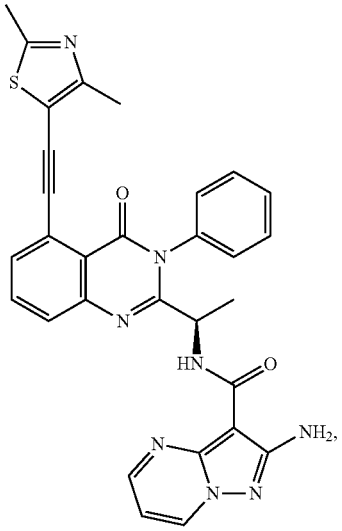
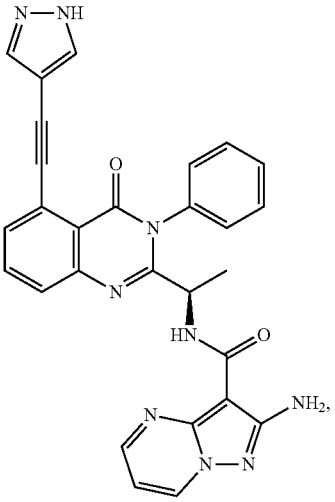
Compound 2076r	
Compound 2077r	
Compound 2078r	

TABLE 13-continued

Compound 2079r



Compound 2080r



Compound 2081r

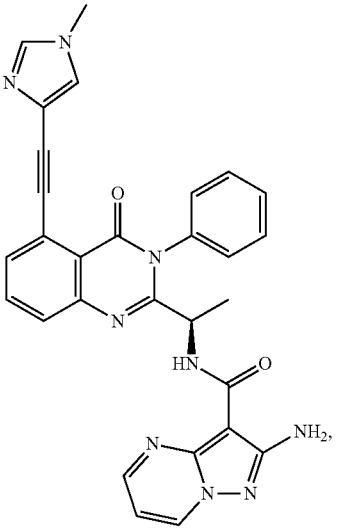
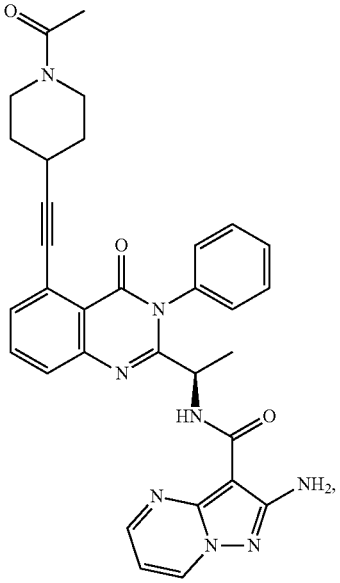


TABLE 13-continued

Compound 2082r



Compound 2083r

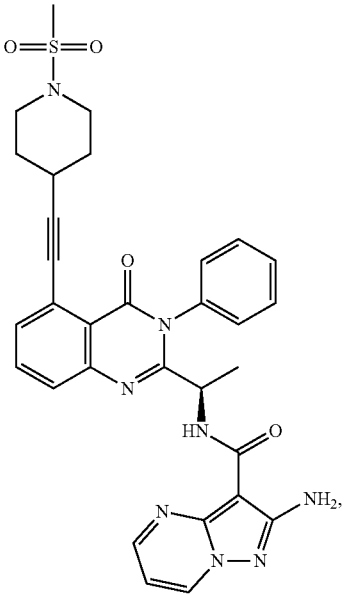
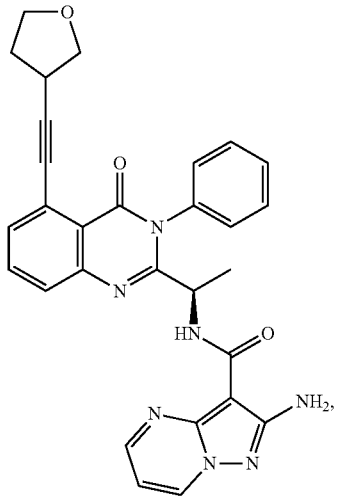
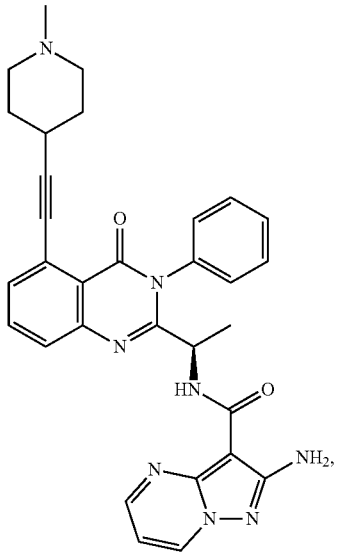


TABLE 13-continued

Compound 2084r



Compound 2085r



Compound 2086r

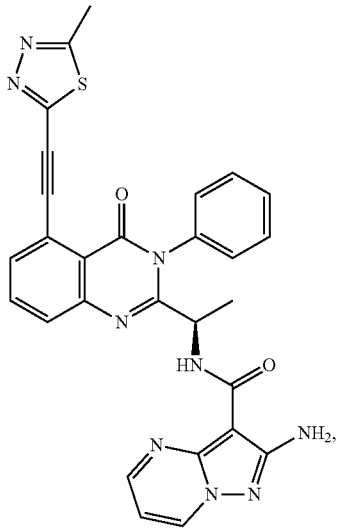
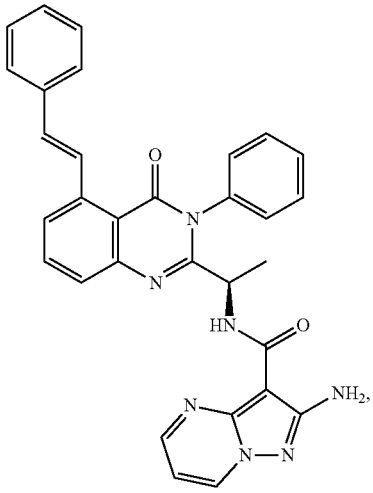
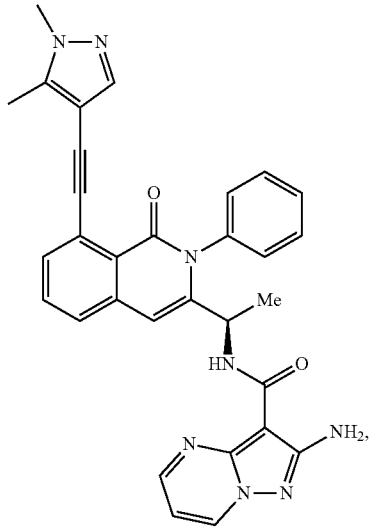


TABLE 13-continued

Compound 2087r



Compound 2088r



Compound 2089r

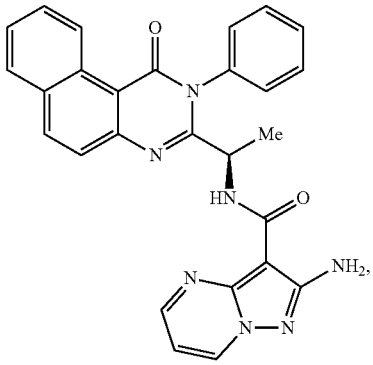
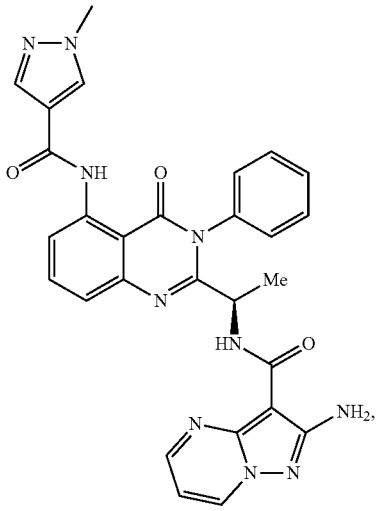
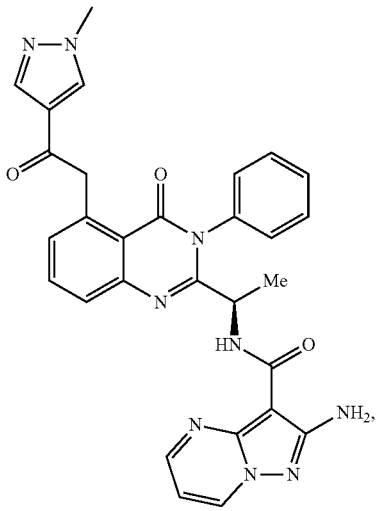


TABLE 13-continued

Compound 2090r



Compound 2091r



Compound 2092r

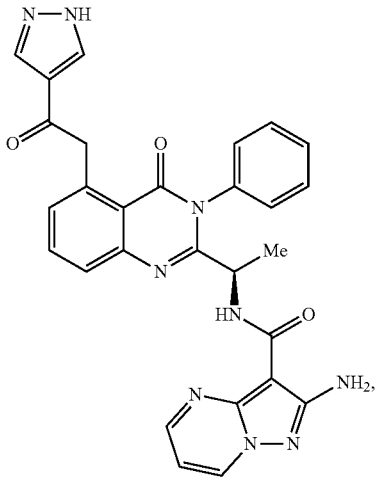
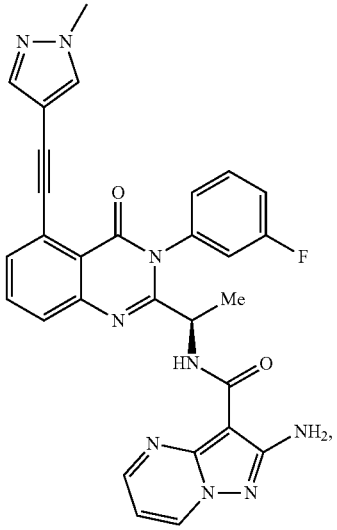
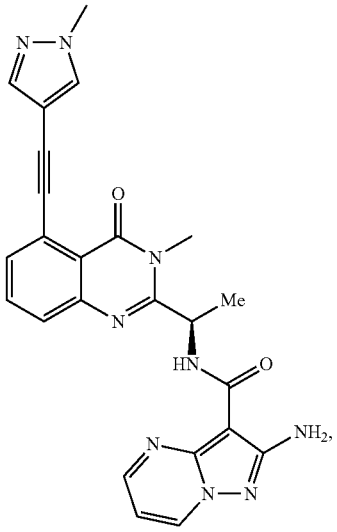


TABLE 13-continued

Compound 2093r



Compound 2094r



Compound 2095r

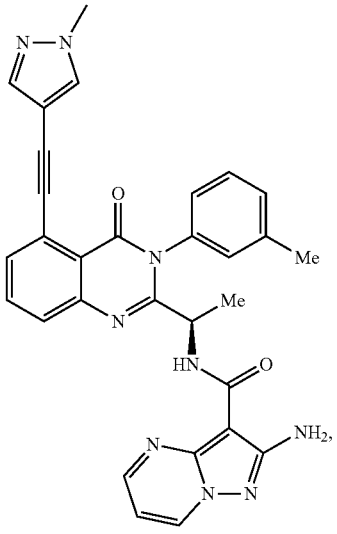


TABLE 13-continued

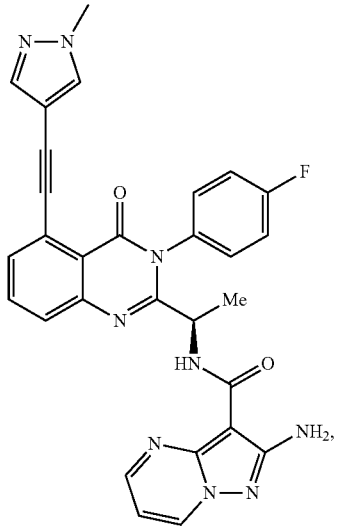
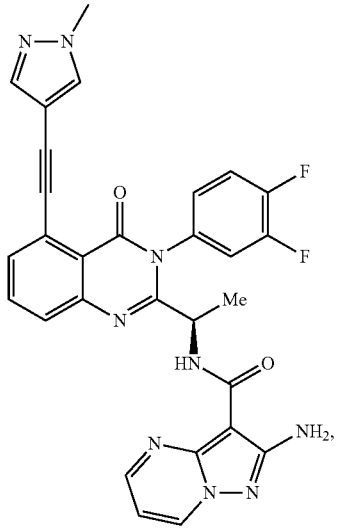
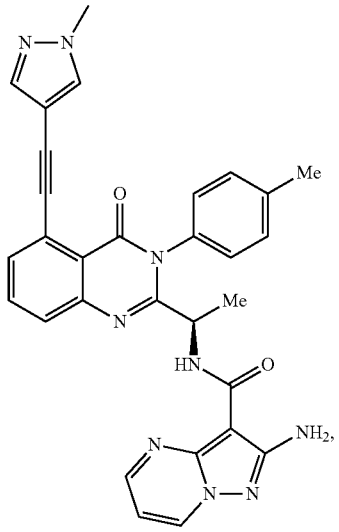
Compound 2096r	
Compound 2097r	
Compound 2098r	

TABLE 13-continued

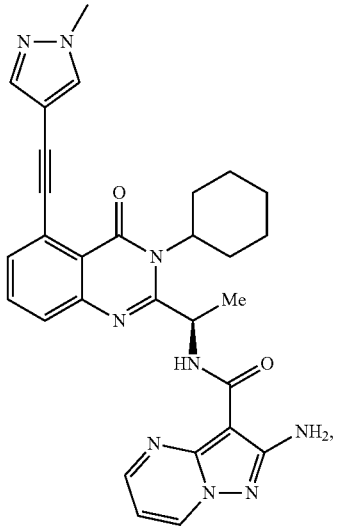
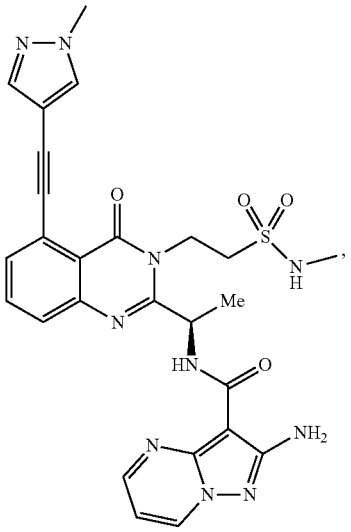
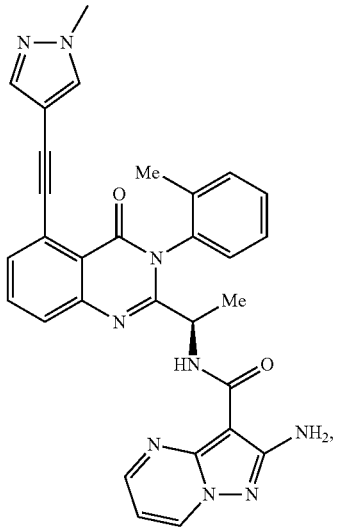
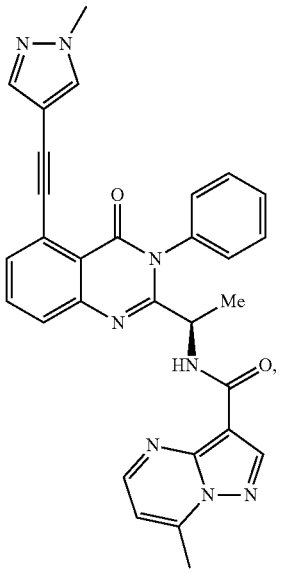
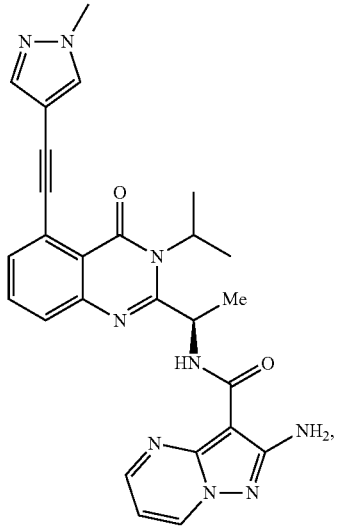
Compound 2099r	
Compound 2100r	
Compound 2101r	

TABLE 13-continued

Compound 2102r



Compound 2103r



Compound 2104r

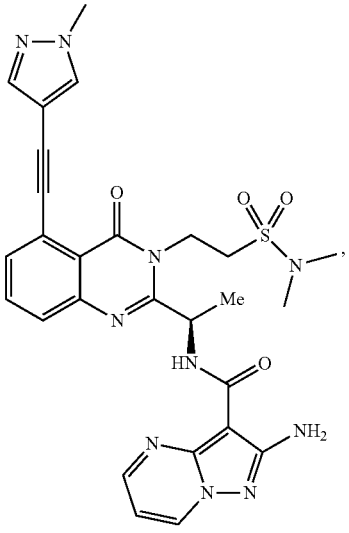
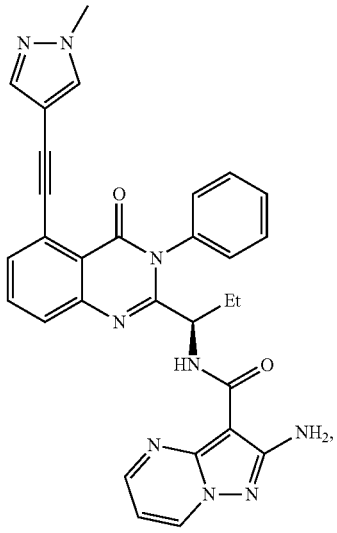
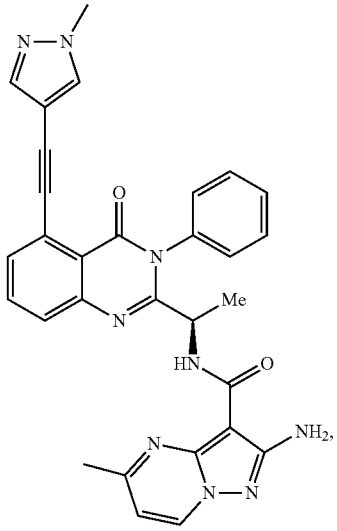


TABLE 13-continued

Compound 2105r



Compound 2106r



Compound 2108r

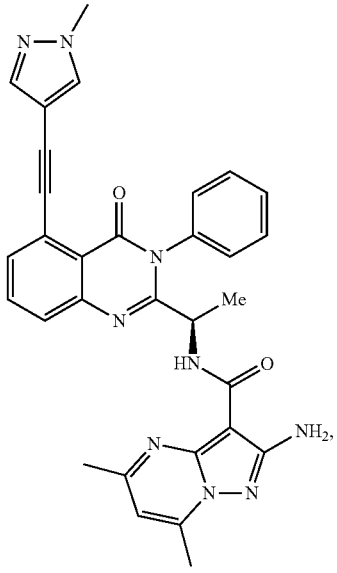


TABLE 13-continued

Compound 2109r

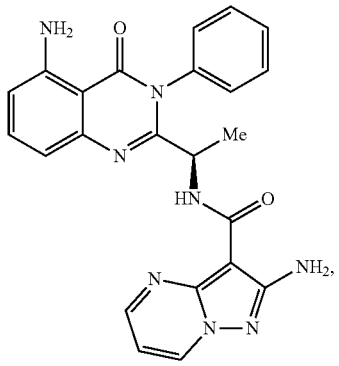
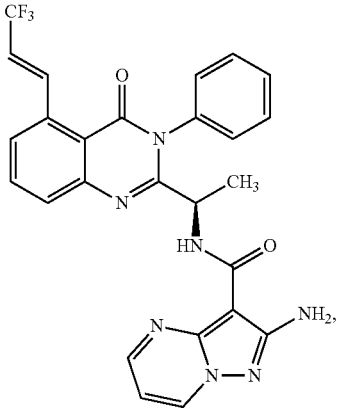


TABLE 14

Compound 3001r



Compound 3002r

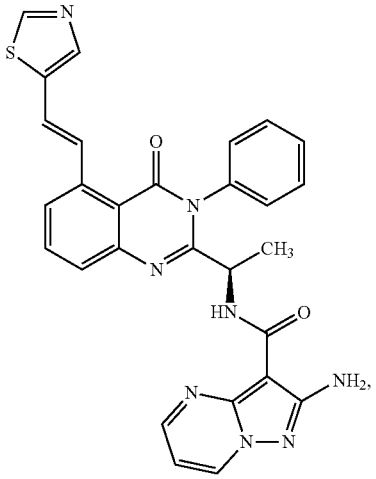
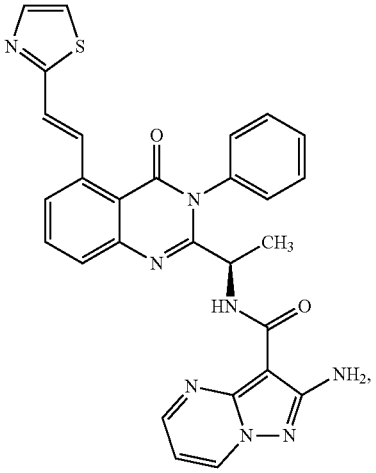
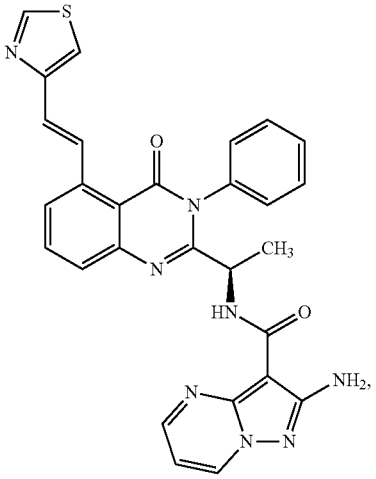


TABLE 14-continued

Compound 3003r



Compound 3004r



Compound 3005r

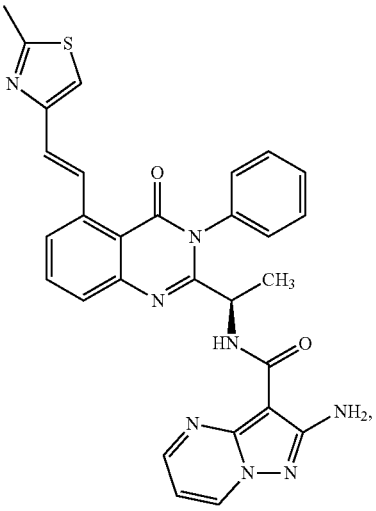
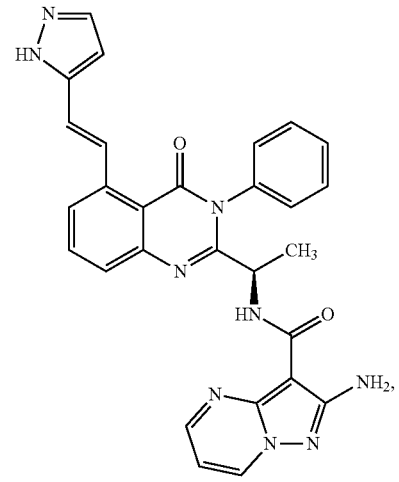
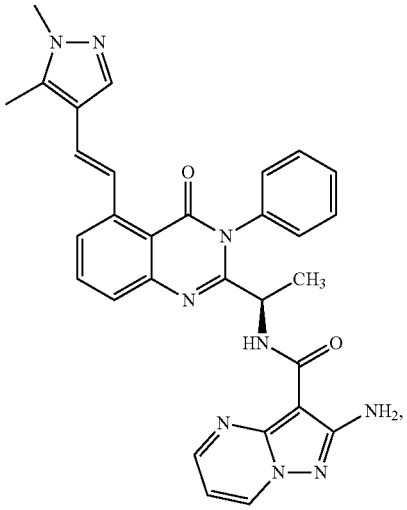


TABLE 14-continued

Compound 3006r



Compound 3007r



Compound 3008r

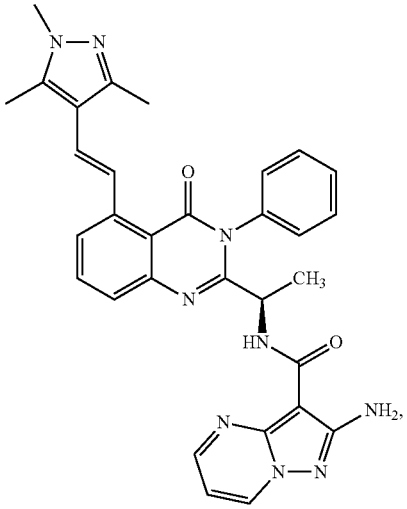
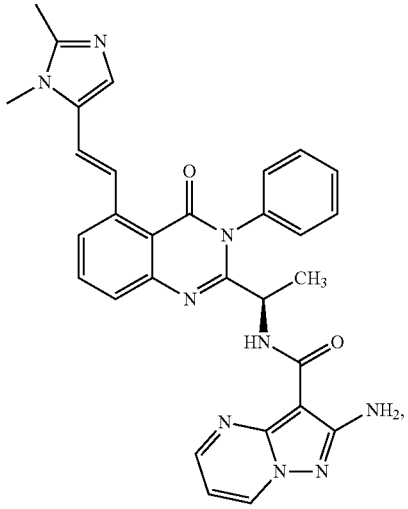
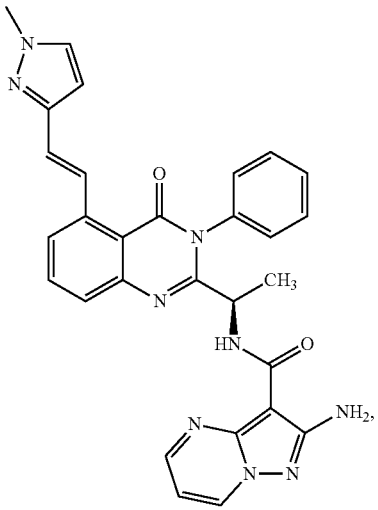


TABLE 14-continued

Compound 3009r



Compound 3010r



Compound 3011r

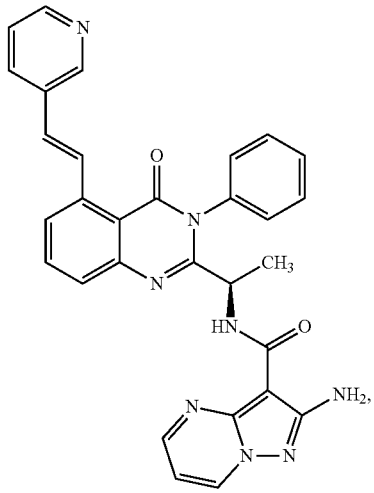
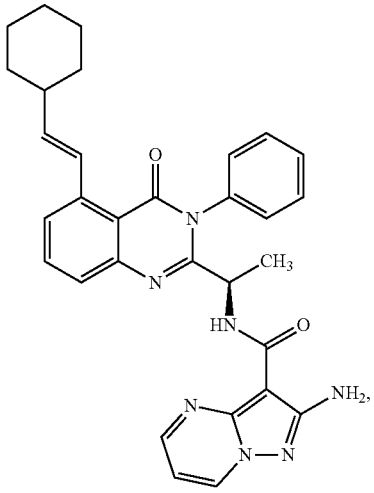
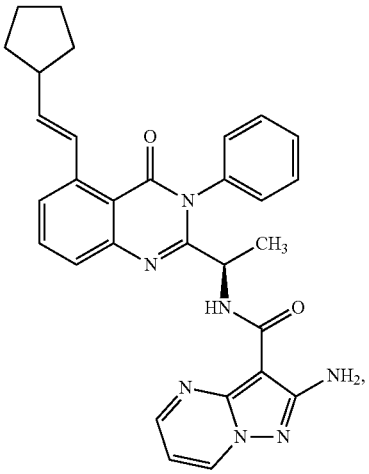


TABLE 14-continued

Compound 3012r



Compound 3013r



Compound 3014r

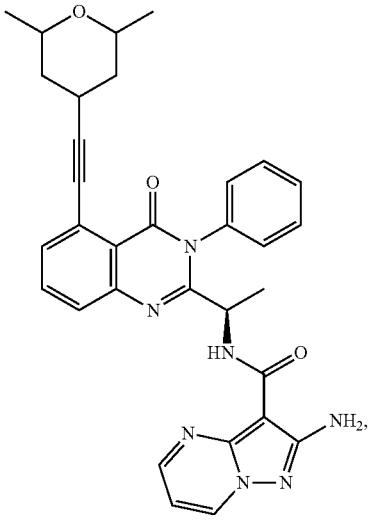
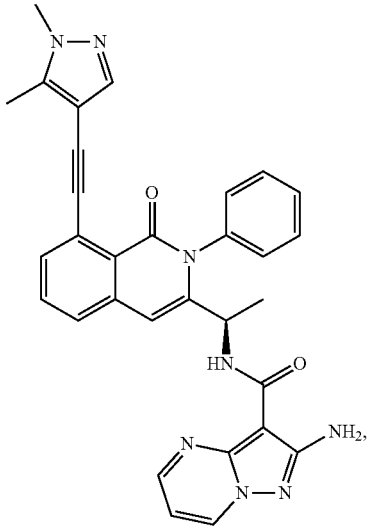
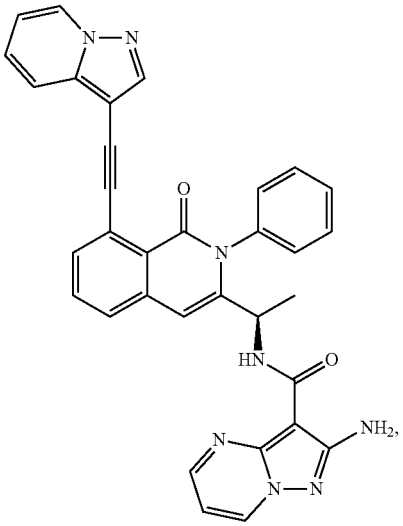


TABLE 14-continued

Compound 3015r



Compound 3016r



Compound 3017r

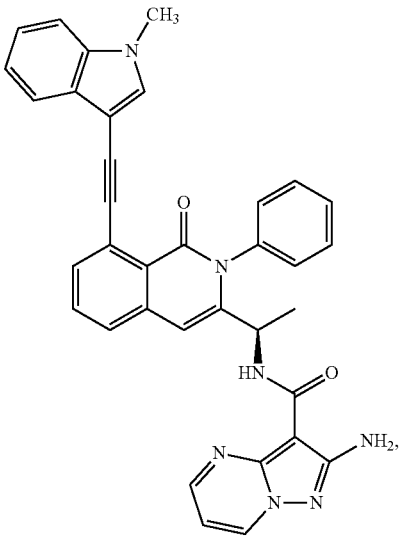


TABLE 14-continued

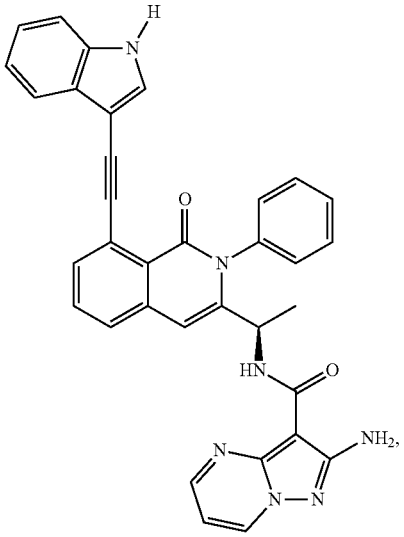
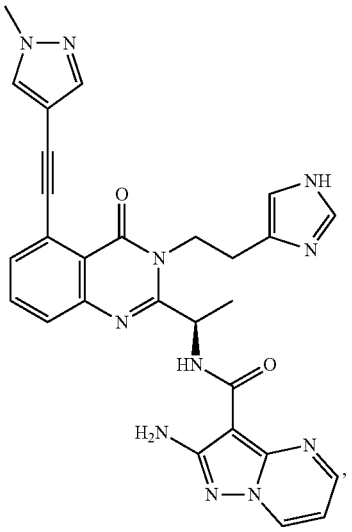
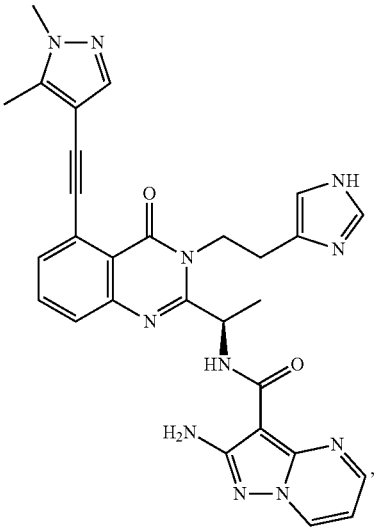
Compound 3018r	
Compound 3045r	
Compound 3046r	

TABLE 14-continued

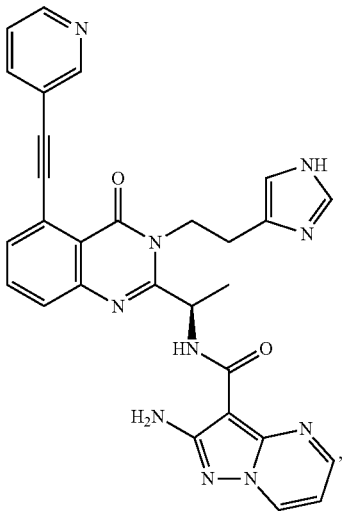
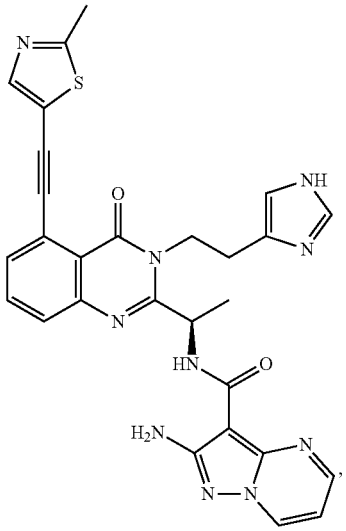
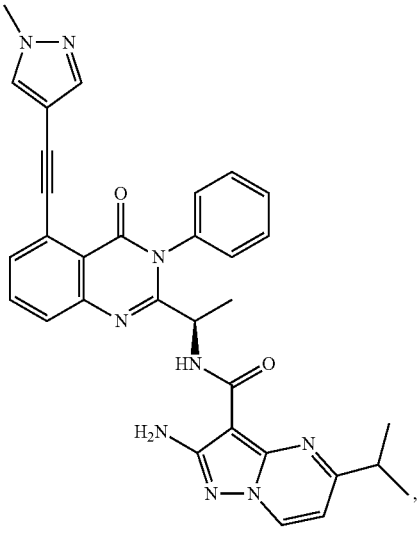
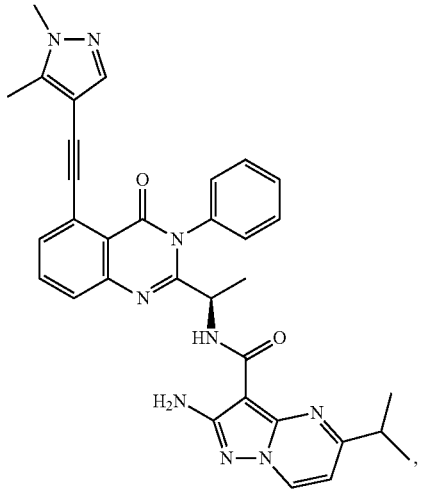
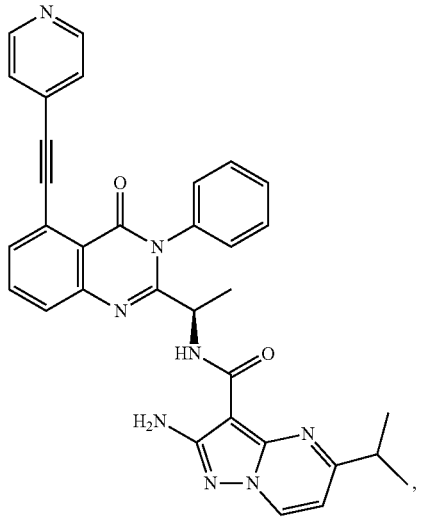
Compound 3047r	
Compound 3048r	
Compound 3049r	

TABLE 14-continued

Compound 3050r



Compound 3051r



Compound 3052r

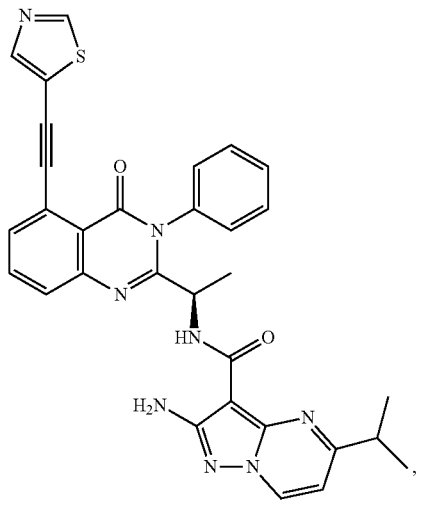
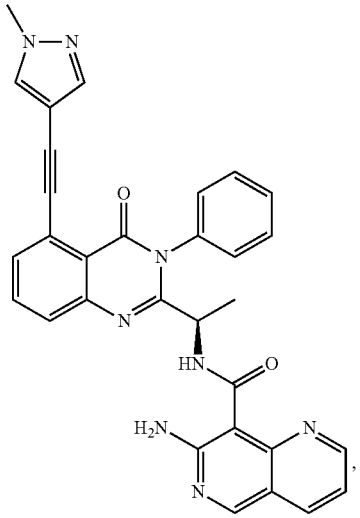
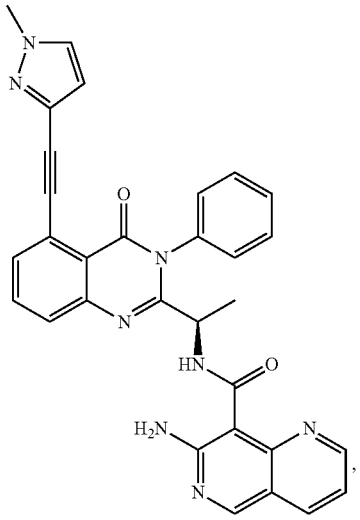


TABLE 14-continued

Compound 3053r



Compound 3054r



Compound 3055r

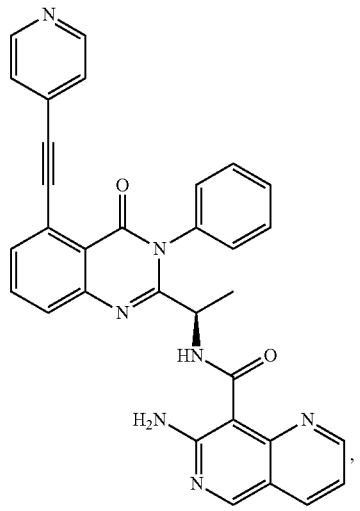
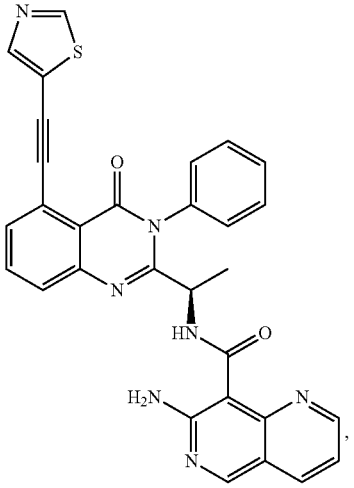
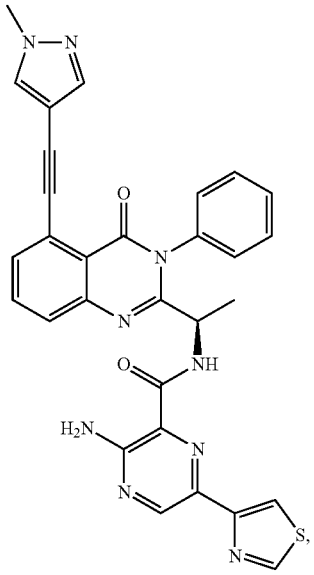


TABLE 14-continued

Compound 3056r



Compound 3057r



Compound 3058r

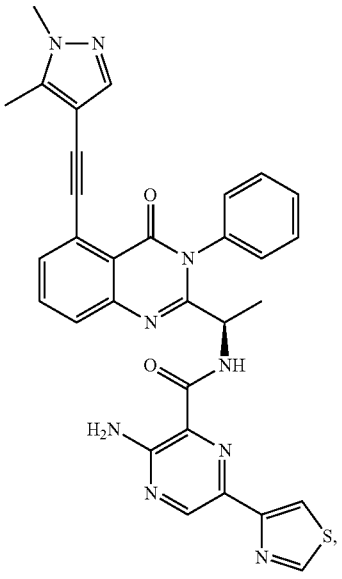
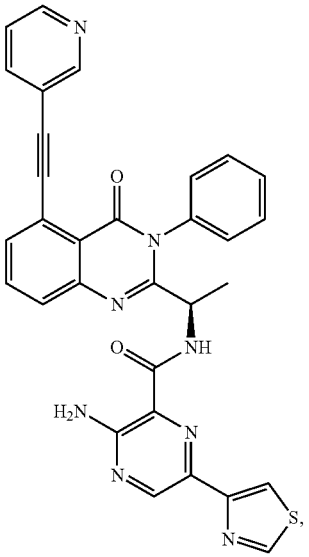


TABLE 14-continued

Compound 3059r



Compound 3060r

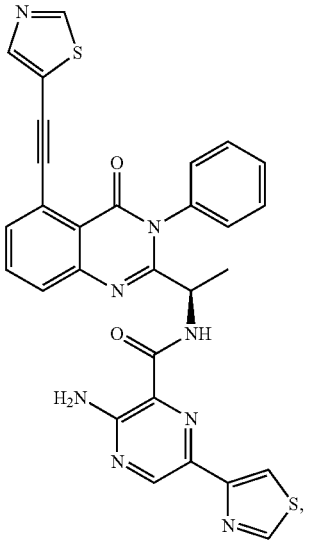
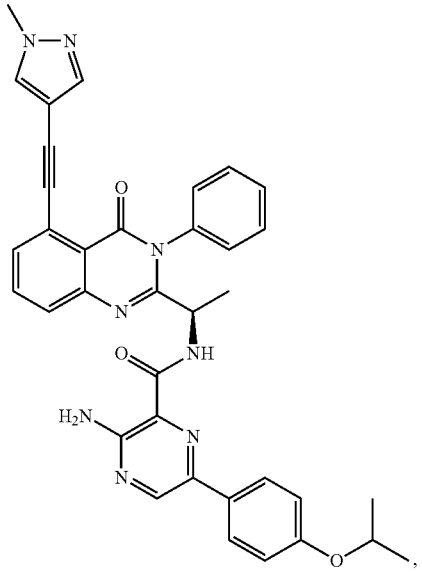


TABLE 14-continued

Compound 3061r



Compound 3062r

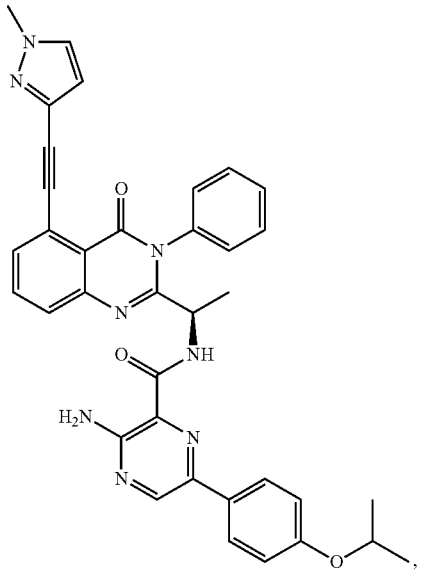
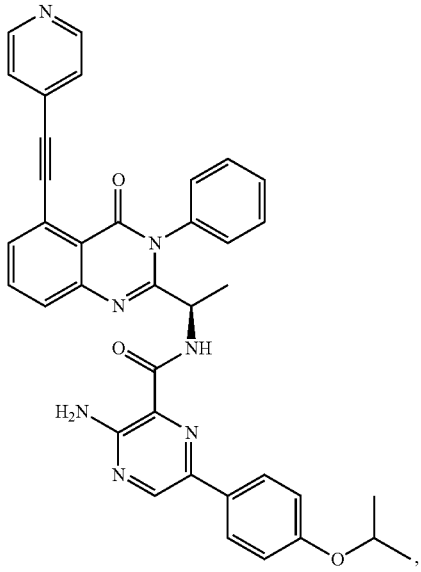


TABLE 14-continued

Compound 3063r



Compound 3064r

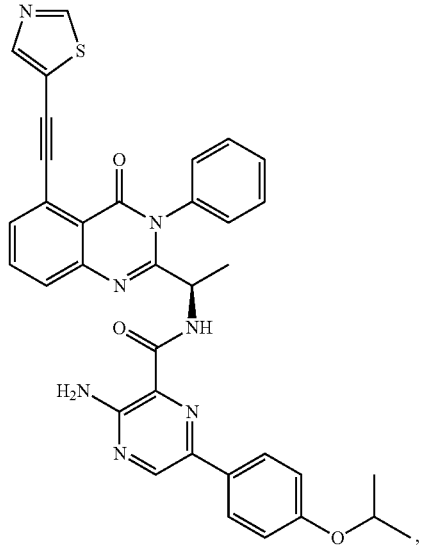


TABLE 14-continued

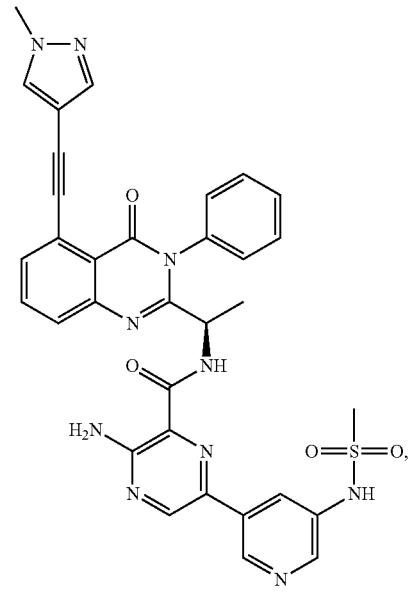
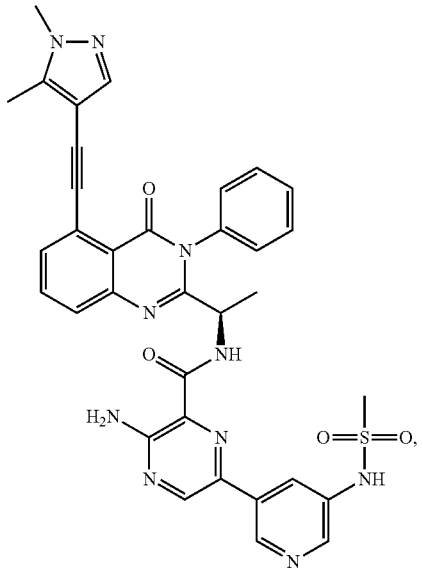
Compound 3065r	
Compound 3066r	

TABLE 14-continued

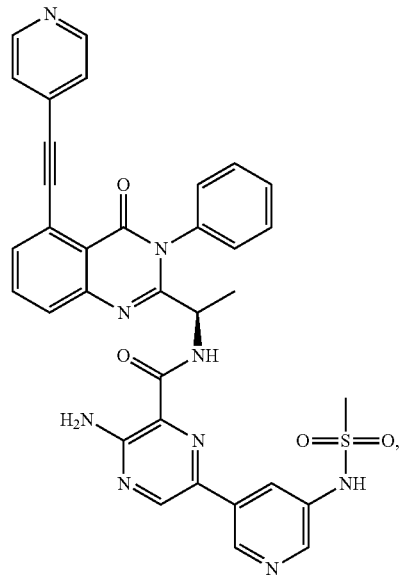
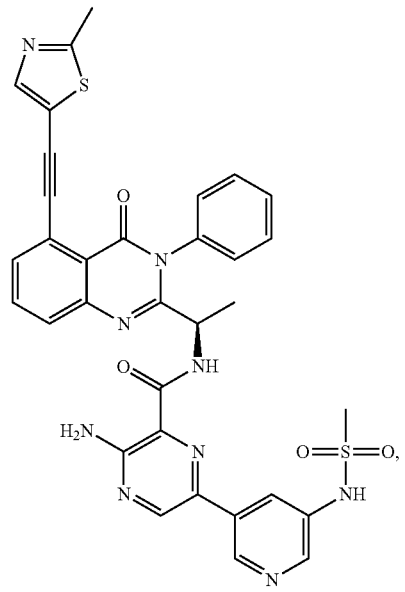
Compound 3067r	
Compound 3068r	

TABLE 14-continued

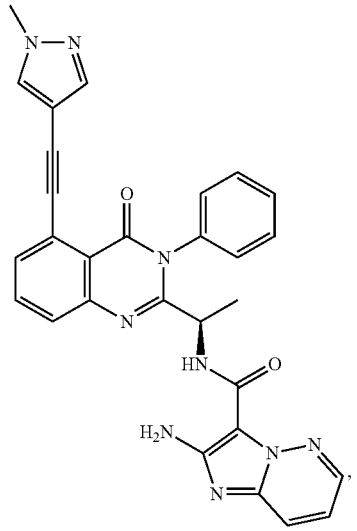
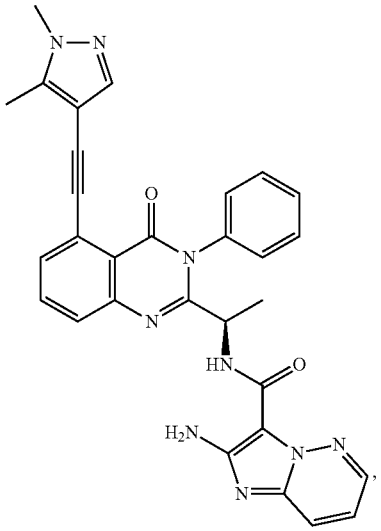
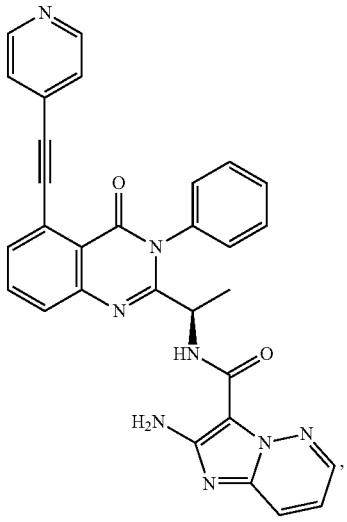
Compound 3069r	
Compound 3070r	
Compound 3071r	

TABLE 14-continued

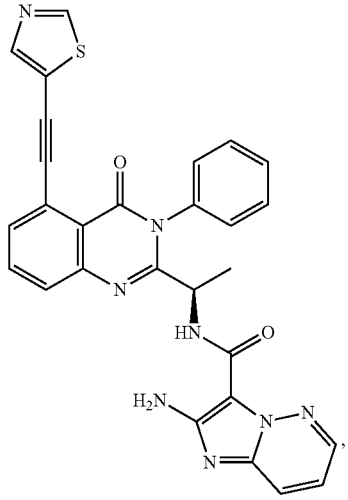
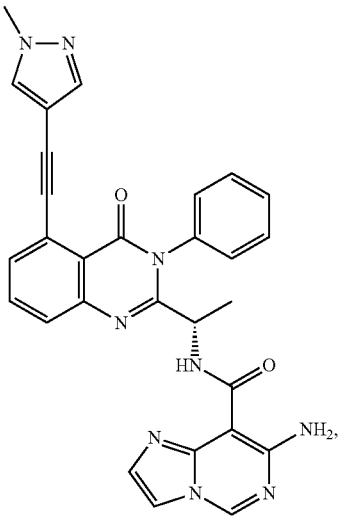
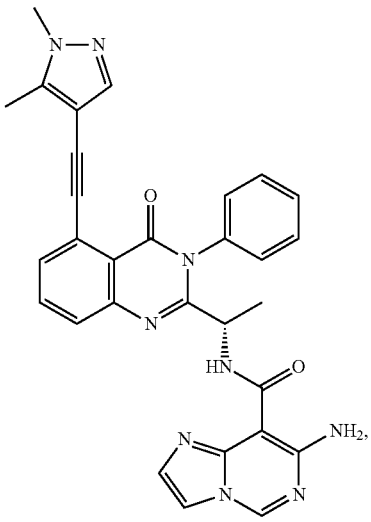
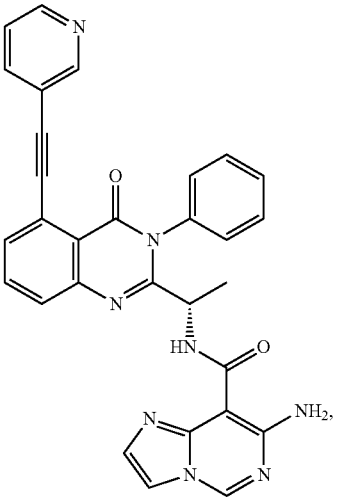
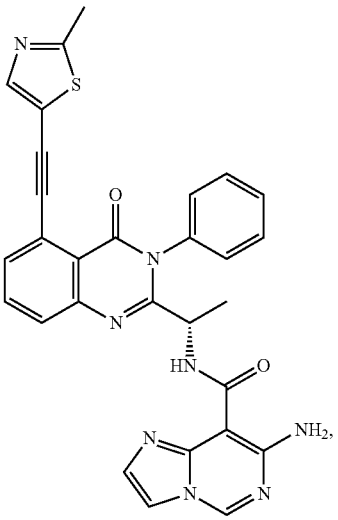
Compound 3072r	
Compound 3073r	
Compound 3074r	

TABLE 14-continued

Compound 3075r



Compound 3076r



Compound 3077r

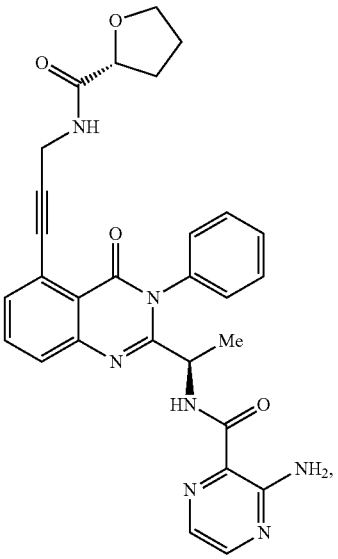
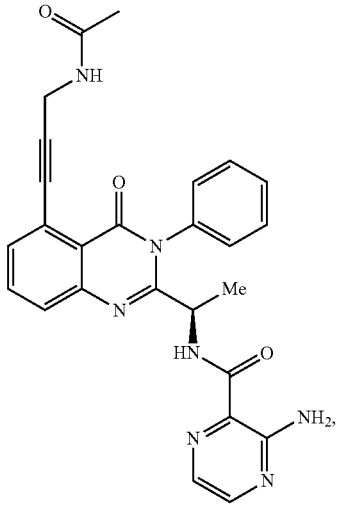
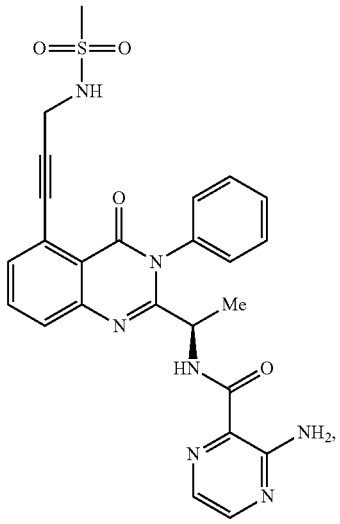


TABLE 14-continued

Compound 3078r



Compound 3079r



Compound 3080r

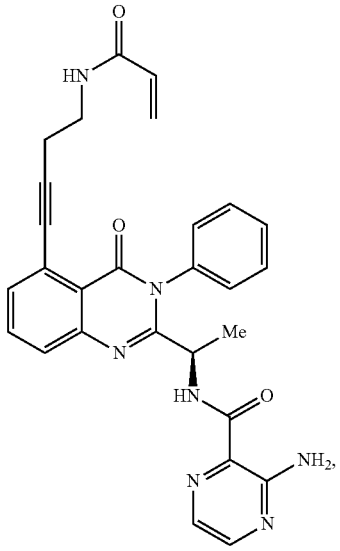
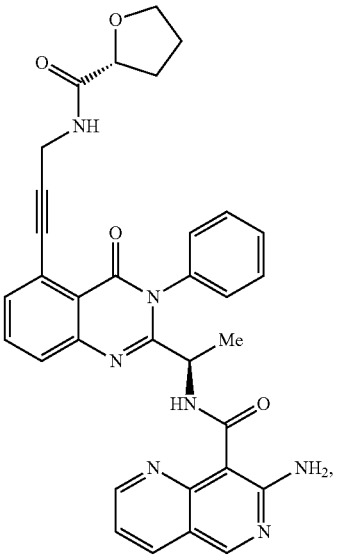
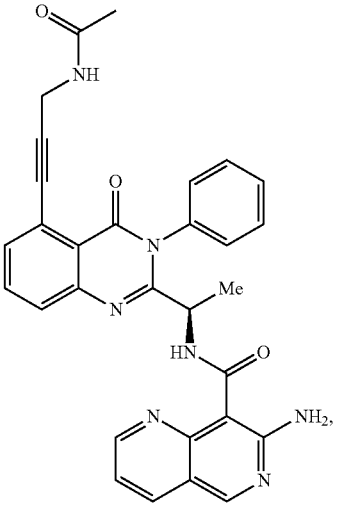


TABLE 14-continued

Compound 3081r



Compound 3082r



Compound 3083r

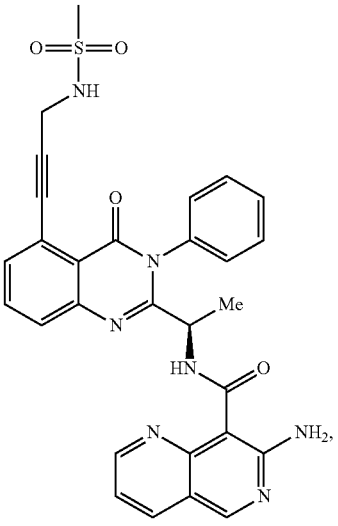
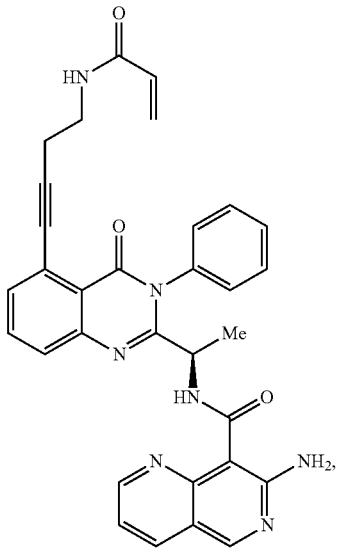
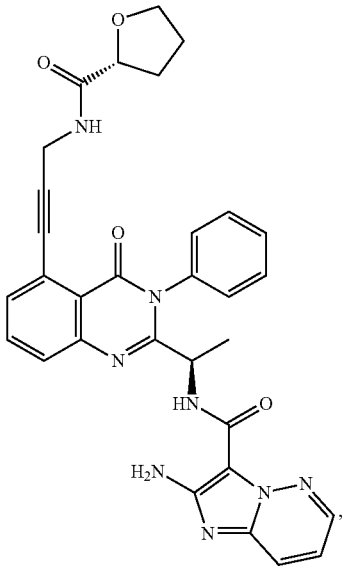


TABLE 14-continued

Compound 3084r



Compound 3085r



Compound 3086r

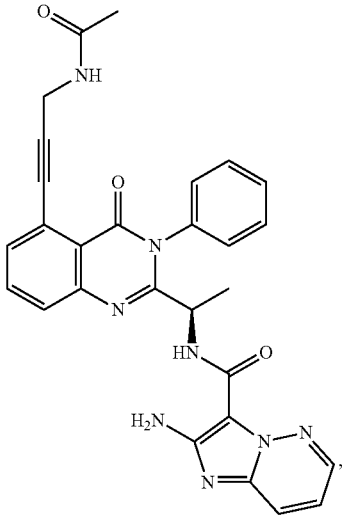


TABLE 14-continued

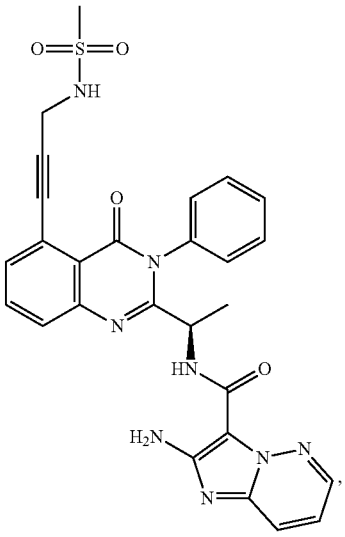
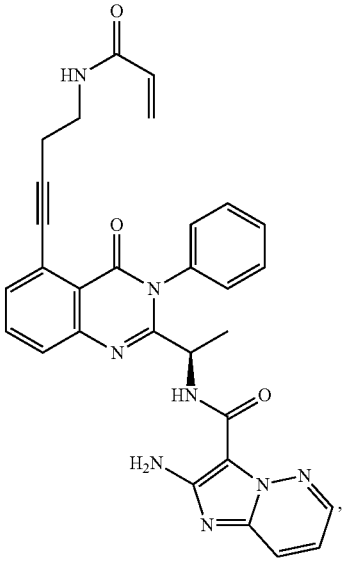
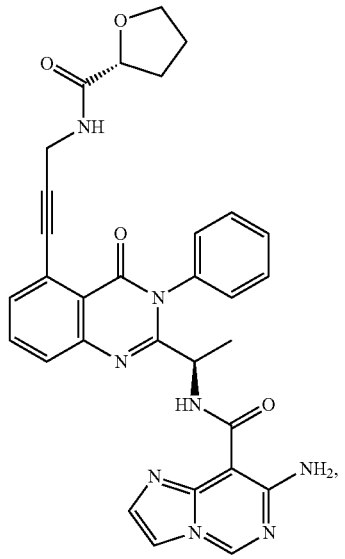
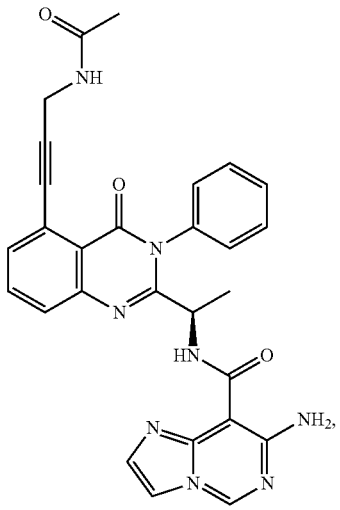
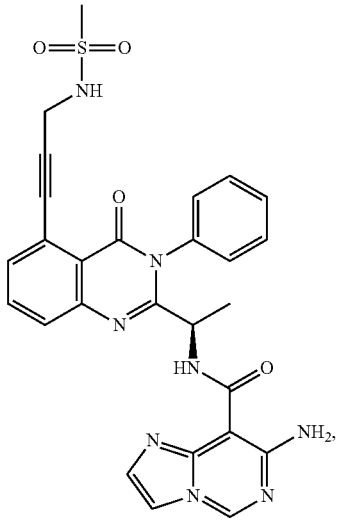
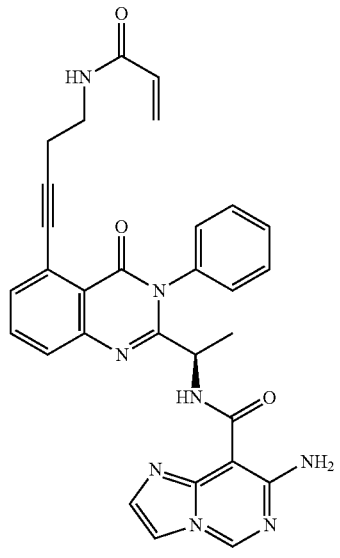
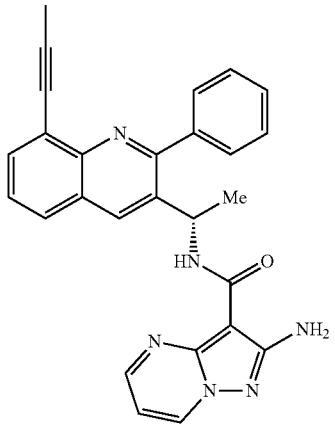
Compound 3087r	
Compound 3088r	
Compound 3089r	

TABLE 14-continued

Compound 3090r	
Compound 3091r	
Compound 3092r	

In some embodiments, the compound provided herein is:



or a pharmaceutically acceptable form thereof.

In some embodiments, one or more compounds described herein bind to a PI3 kinase (e.g., bind selectively). In some embodiments, one or more compounds described herein bind selectively to a γ- or δ-subtype of a PI3 kinase. In some embodiments, one or more compounds described herein bind selectively to a γ-subtype of a PI3 kinase. In some embodiments, one or more compounds described herein bind selectively to a δ-subtype of a PI3 kinase. In one embodiment, one or more compounds described herein selectively binds to δ over γ. In one embodiment, one or more compounds described herein selectively binds to γ over δ.

In certain embodiments provided herein are methods of treating or preventing a PI3K mediated disorder in a subject, the method comprising administering a therapeutically effective amount of a compound provided herein or composition provided herein to said subject. In certain embodiments, provided herein is the use of a compound provided herein in the manufacture of a medicament for treating or preventing a PI3K mediated disorder in a subject. In certain embodiments, a compound provided herein is for use in treating or preventing a PI3K mediated disorder in a subject. In certain embodiments, the disorder is cancer, an inflammatory disease, or an auto-immune disease. In certain embodiments, the PI3K mediated disorder is a PI3K-γ mediated disorder. In certain embodiments, the PI3K mediated disorder is a PI3K-δ mediated disorder. In certain embodiments, provided herein are methods for selectively inhibiting PI3K gamma over PI3K delta in a cell or subject comprising contacting the cell or administering to the subject a compound provided herein. In certain embodiments, provided wherein are methods for selectively inhibiting PI3K gamma over PI3K delta in a cell or subject comprising contacting the cell or administering to the subject

(i) a compound selected from compound 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, 88, and 89; or

(ii) a compound is selected from compound 1, 3, 6, 10, 11, 12, 16, 18, 20, 22, 25, 28, 34, 39, 42, 43, 53, 55, 59, 64, 65, 66, 67, 70, 76, 78, 82, 83, 84, 85, 86, and 90; or

(iii) a compound selected from compound 8, 13, 15, 23, 29, 33, 45, 51, 54, 57, and 68; or

(iv) a compound selected from compound 5, 14, 24, 31, 36, 46, 50, 69, 72, 74, and 91.

In certain embodiments, the compound is selected from compound 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, 88, and 89. In certain embodiments, the compound is selected from compound 1, 3, 6, 10, 11, 12, 16, 18, 20, 22, 25, 28, 34, 39, 42, 43, 53, 55, 59, 64, 65, 66, 67, 70, 76, 78, 82, 83, 84, 85, 86, and 90. In certain embodiments, the compound is selected from compound 8, 13, 15, 23, 29, 33, 45, 51, 54, 57, and 68. In certain embodiments, the compound is selected from compound 5, 14, 24, 31, 36, 46, 50, 69, 72, 74, and 91.

In certain embodiments, provided herein are methods of synthesizing a compound the compounds provided herein. Provided herein are methods of making a PI3K-γ selective compound comprising synthesizing a compound containing both (a) a non-terminal alkyne substituted bicyclic heterocyclic group and (b) an amido group. In some embodiments, the compound selectively binds to PI3K-γ over PI3K-δ.

In some embodiments, the IC_{50} of a compound provided herein for p110α, p110β, p110γ, or p110δ is less than about 1 μM, less than about 100 nM, less than about 50 nM, less than about 10 nM, less than 1 nM, or even less than about 0.5 nM.

In some embodiments, non-limiting exemplary compounds exhibit one or more functional characteristics disclosed herein. For example, one or more compounds provided herein bind specifically to a PI3 kinase. In some embodiments, the IC_{50} of a compound provided herein for p110α, p110β, p110γ, or p110δ is less than about 1 μM, less than about 100 nM, less than about 50 nM, less than about 10 nM, less than about 1 nM, less than about 0.5 nM, less than about 100 pM, or less than about 50 pM.

In some embodiments, one or more of the compounds provided herein can selectively inhibit one or more members of type I or class I phosphatidylinositol 3-kinases (PI3-kinase) with an IC_{50} value of about 100 nM, about 50 nM, about 10 nM, about 5 nM, about 100 pM, about 10 pM, or about 1 pM, or less, as measured in an in vitro kinase assay.

In some embodiments, one or more of the compounds provided herein can selectively inhibit one or two members of type I or class I phosphatidylinositol 3-kinases (PI3-kinase), such as, PI3-kinase α, PI3-kinase β, PI3-kinase γ, and PI3-kinase δ. In some aspects, some of the compounds provided herein selectively inhibit PI3-kinase δ as compared to all other type I PI3-kinases. In other aspects, some of the compounds provided herein selectively inhibit PI3-kinase δ and PI3-kinase γ as compared to the rest of the type I PI3-kinases. In other aspects, some of the compounds provided herein selectively inhibit PI3-kinase γ as compared to all other type I PI3-kinases.

In yet another aspect, an inhibitor that selectively inhibits one or more members of type I PI3-kinases, or an inhibitor that selectively inhibits one or more type I PI3-kinase mediated signaling pathways, alternatively can be understood to refer to a compound that exhibits a 50% inhibitory concentration (IC_{50}) with respect to a given type I PI3-kinase, that is at least about 10-fold, at least about 20-fold, at least about 50-fold, at least about 100-fold, at least about 200-fold, at least about 500-fold, at least about 1000-fold, at least about 2000-fold, at least about 5000-fold, or at least about 10,000-fold, lower than the inhibitor's IC_{50} with respect to the rest of the other type I PI3-kinases. In one embodiment, an inhibitor selectively inhibits PI3-kinase δ as compared to PI3-kinase with at least about 10-fold lower IC_{50} for PI3-kinase δ. In certain embodiments, the IC_{50} for PI3-kinase δ is below about 100 nM, while the IC_{50} for PI3-kinase β is above about 1000 nM. In certain embodiments, the IC_{50} for PI3-kinase δ is below about 50 nM, while the IC_{50} for PI3-kinase β is above about 5000 nM. In certain embodiments, the IC_{50} for PI3-kinase δ is below about 10 nM, while the IC_{50} for PI3-kinase β is above about 1000 nM, above about 5,000 nM, or above

about 10,000 nM. In one embodiment, an inhibitor selectively inhibits PI3-kinase γ as compared to PI3-kinase with at least about 10-fold lower IC_{50} for PI3-kinase γ. In certain embodiments, the IC_{50} for PI3-kinase γ is below about 100 nM, while the IC_{50} for PI3-kinase β is above about 1000 nM. In certain embodiments, the IC_{50} for PI3-kinase γ is below about 50 nM, while the IC_{50} for PI3-kinase β is above about 5000 nM. In certain embodiments, the IC_{50} for PI3-kinase γ is below about 10 nM, while the IC_{50} for PI3-kinase β is above about 1000 nM, above about 5,000 nM, or above about 10,000 nM.

Pharmaceutical Compositions

In some embodiments, provided herein are pharmaceutical compositions comprising a compound as disclosed herein, or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or a pharmaceutically acceptable form thereof (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives), and a pharmaceutically acceptable excipient, diluent, or carrier, including inert solid diluents and fillers, sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. In some embodiments, a pharmaceutical composition described herein includes a second active agent such as an additional therapeutic agent, (e.g., a chemotherapeutic).

1. Formulations

Pharmaceutical compositions can be specially formulated for administration in solid or liquid form, including those adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets (e.g., those targeted for buccal, sublingual, and systemic absorption), capsules, boluses, powders, granules, pastes for application to the tongue, and intraduodenal routes; parenteral administration, including intravenous, intraarterial, subcutaneous, intramuscular, intravascular, intraperitoneal or infusion as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; intravaginally or intrarectally, for example, as a pessary, cream, stent or foam; sublingually; ocularly; pulmonarily; local delivery by catheter or stent; intrathecally, or nasally.

Examples of suitable aqueous and nonaqueous carriers which can be employed in pharmaceutical compositions include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions can also contain adjuvants such as preservatives, wetting agents, emulsifying agents, dispersing agents, lubricants, and/or antioxidants. Prevention of the action of microorganisms upon the compounds described herein can be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It can also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

Methods of preparing these formulations or compositions include the step of bringing into association a compound described herein and/or the chemotherapeutic with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound as disclosed herein with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Preparations for such pharmaceutical compositions are well-known in the art. See, e.g., Anderson, Philip O.; Knoben, James E.; Troutman, William G, eds., *Handbook of Clinical Drug Data*, Tenth Edition, McGraw-Hill, 2002; Pratt and Taylor, eds., *Principles of Drug Action*, Third Edition, Churchill Livingston, N.Y., 1990; Katzung, ed., *Basic and Clinical Pharmacology*, Twelfth Edition, McGraw Hill, 2011; Goodman and Gilman, eds., *The Pharmacological Basis of Therapeutics*, Tenth Edition, McGraw Hill, 2001; *Remingtons Pharmaceutical Sciences,* 20th Ed., Lippincott Williams & Wilkins., 2000; Martindale, *The Extra Pharmacopoeia,* Thirty-Second Edition (The Pharmaceutical Press, London, 1999); all of which are incorporated by reference herein in their entirety. Except insofar as any conventional excipient medium is incompatible with the compounds provided herein, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, the excipient's use is contemplated to be within the scope of this disclosure.

In some embodiments, the concentration of one or more of the compounds provided in the disclosed pharmaceutical compositions is less than about 100%, about 90%, about 80%, about 70%, about 60%, about 50%, about 40%, about 30%, about 20%, about 19%, about 18%, about 17%, about 16%, about 15%, about 14%, about 13%, about 12%, about 11%, about 10%, about 9%, about 8%, about 7%, about 6%, about 5%, about 4%, about 3%, about 2%, about 1%, about 0.5%, about 0.4%, about 0.3%, about 0.2%, about 0.1%, about 0.09%, about 0.08%, about 0.07%, about 0.06%, about 0.05%, about 0.04%, about 0.03%, about 0.02%, about 0.01%, about 0.009%, about 0.008%, about 0.007%, about 0.006%, about 0.005%, about 0.004%, about 0.003%, about 0.002%, about 0.001%, about 0.0009%, about 0.0008%, about 0.0007%, about 0.0006%, about 0.0005%, about 0.0004%, about 0.0003%, about 0.0002%, or about 0.0001%, w/w, w/v or v/v.

In some embodiments, the concentration of one or more of the compounds as disclosed herein is greater than about 90%, about 80%, about 70%, about 60%, about 50%, about 40%, about 30%, about 20%, about 19.75%, about 19.50%, about 19.25%, about 19%, about 18.75%, about 18.50%, about 18.25%, about 18%, about 17.75%, about 17.50%, about 17.25%, about 17%, about 16.75%, about 16.50%, about 16.25%, about 16%, about 15.75%, about 15.50%, about 15.25%, about 15%, about 14.75%, about 14.50%, about 14.25%, about 14%, about 13.75%, about 13.50%, about 13.25%, about 13%, about 12.75%, about 12.50%, about 12.25%, about 12%, about 11.75%, about 11.50%, about 11.25%, about 11%, about 10.75%, about 10.50%, about 10.25%, about 10%, about 9.75%, about 9.50%, about 9.25%, about 9%, about 8.75%, about 8.50%, about 8.25%, about 8%, about 7.75%, about 7.50%, about 7.25%, about 7%, about 6.75%, about 6.50%, about 6.25%, about 6%, about 5.75%, about 5.50%, about 5.25%, about 5%, about 4.75%, about 4.50%, about 4.25%, about 4%, about 3.75%, about 3.50%, about 3.25%, about 3%, about 2.75%, about 2.50%, about 2.25%, about 2%, about 1.75%, about 1.50%, about 1.25%, about 1%, about 0.5%, about 0.4%, about 0.3%, about 0.2%, about 0.1%, about 0.09%, about 0.08%, about 0.07%, about 0.06%, about 0.05%, about 0.04%, about 0.03%, about 0.02%, about 0.01%, about 0.009%, about 0.008%, about 0.007%, about 0.006%, about 0.005%, about 0.004%, about 0.003%, about 0.002%, about 0.001%, about 0.0009%, about

0.0008%, about 0.0007%, about 0.0006%, about 0.0005%, about 0.0004%, about 0.0003%, about 0.0002%, or about 0.0001%, w/w, w/v, or v/v.

In some embodiments, the concentration of one or more of the compounds as disclosed herein is in the range from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40%, approximately 0.01% to approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately 0.1% to approximately 21%, approximately 0.2% to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8% to approximately 14%, approximately 0.9% to approximately 12%, or approximately 1% to approximately 10%, w/w, w/v or v/v.

In some embodiments, the concentration of one or more of the compounds as disclosed herein is in the range from approximately 0.001% to approximately 10%, approximately 0.01% to approximately 5%, approximately 0.02% to approximately 4.5%, approximately 0.03% to approximately 4%, approximately 0.04% to approximately 3.5%, approximately 0.05% to approximately 3%, approximately 0.06% to approximately 2.5%, approximately 0.07% to approximately 2%, approximately 0.08% to approximately 1.5%, approximately 0.09% to approximately 1%, or approximately 0.1% to approximately 0.9%, w/w, w/v or v/v.

In some embodiments, the amount of one or more of the compounds as disclosed herein is equal to or less than about 10 g, about 9.5 g, about 9.0 g, about 8.5 g, about 8.0 g, about 7.5 g, about 7.0 g, about 6.5 g, about 6.0 g, about 5.5 g, about 5.0 g, about 4.5 g, about 4.0 g, about 3.5 g, about 3.0 g, about 2.5 g, about 2.0 g, about 1.5 g, about 1.0 g, about 0.95 g, about 0.9 g, about 0.85 g, about 0.8 g, about 0.75 g, about 0.7 g, about 0.65 g, about 0.6 g, about 0.55 g, about 0.5 g, about 0.45 g, about 0.4 g, about 0.35 g, about 0.3 g, about 0.25 g, about 0.2 g, about 0.15 g, about 0.1 g, about 0.09 g, about 0.08 g, about 0.07 g, about 0.06 g, about 0.05 g, about 0.04 g, about 0.03 g, about 0.02 g, about 0.01 g, about 0.009 g, about 0.008 g, about 0.007 g, about 0.006 g, about 0.005 g, about 0.004 g, about 0.003 g, about 0.002 g, about 0.001 g, about 0.0009 g, about 0.0008 g, about 0.0007 g, about 0.0006 g, about 0.0005 g, about 0.0004 g, about 0.0003 g, about 0.0002 g, or about 0.0001 g.

In some embodiments, the amount of one or more of the compounds as disclosed herein is more than about 0.0001 g, about 0.0002 g, about 0.0003 g, about 0.0004 g, about 0.0005 g, about 0.0006 g, about 0.0007 g, about 0.0008 g, about 0.0009 g, about 0.001 g, about 0.0015 g, about 0.002 g, about 0.0025 g, about 0.003 g, about 0.0035 g, about 0.004 g, about 0.0045 g, about 0.005 g, about 0.0055 g, about 0.006 g, about 0.0065 g, about 0.007 g, about 0.0075 g, about 0.008 g, about 0.0085 g, about 0.009 g, about 0.0095 g, about 0.01 g, about 0.015 g, about 0.02 g, about 0.025 g, about 0.03 g, about 0.035 g, about 0.04 g, about 0.045 g, about 0.05 g, about 0.055 g, about 0.06 g, about 0.065 g, about 0.07 g, about 0.075 g, about 0.08 g, about 0.085 g, about 0.09 g, about 0.095 g, about 0.1 g, about 0.15 g, about 0.2 g, about 0.25 g, about 0.3 g, about 0.35 g, about 0.4 g, about 0.45 g, about 0.5 g, about 0.55 g, about 0.6 g, about 0.65 g, about 0.7 g, about 0.75 g, about 0.8 g, about 0.85 g, about 0.9 g, about 0.95 g, about 1 g, about 1.5 g, about 2 g, about 2.5 g, about 3 g, about 3.5 g, about 4 g, about 4.5 g, about 5 g, about 5.5 g, about 6 g, about 6.5 g, about 7 g, about 7.5 g, about 8 g, about 8.5 g, about 9 g, about 9.5 g, or about 10 g.

In some embodiments, the amount of one or more of the compounds as disclosed herein is in the range of about 0.0001 to about 10 g, about 0.0005 to about 9 g, about 0.001 to about 8 g, about 0.005 to about 7 g, about 0.01 to about 6 g, about 0.05 to about 5 g, about 0.1 to about 4 g, about 0.5 to about 4 g, or about 1 to about 3 g.

1A. Formulations for Oral Administration

In some embodiments, provided herein are pharmaceutical compositions for oral administration containing a compound as disclosed herein, and a pharmaceutical excipient suitable for oral administration. In some embodiments, provided herein are pharmaceutical compositions for oral administration containing: (i) an effective amount of a disclosed compound; optionally (ii) an effective amount of one or more second agents; and (iii) one or more pharmaceutical excipients suitable for oral administration. In some embodiments, the pharmaceutical composition further contains: (iv) an effective amount of a third agent.

In some embodiments, the pharmaceutical composition can be a liquid pharmaceutical composition suitable for oral consumption. Pharmaceutical compositions suitable for oral administration can be presented as discrete dosage forms, such as capsules, cachets, or tablets, or liquids or aerosol sprays each containing a predetermined amount of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such dosage forms can be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient into association with the carrier, which constitutes one or more ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient such as, but not limited to, a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The present disclosure further encompasses anhydrous pharmaceutical compositions and dosage forms comprising an active ingredient, since water can facilitate the degradation of some compounds. For example, water can be added (e.g., about 5%) in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. Anhydrous pharmaceutical compositions and dosage forms can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. For example, pharmaceutical compositions and dosage forms which contain lactose can be made anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected. An anhydrous pharmaceutical composition can be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous pharmaceutical compositions can be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable

packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

An active ingredient can be combined in an intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration. In preparing the pharmaceutical compositions for an oral dosage form, any of the usual pharmaceutical media can be employed as carriers, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions, and elixirs) or aerosols; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used in the case of oral solid preparations, in some embodiments without employing the use of lactose. For example, suitable carriers include powders, capsules, and tablets, with the solid oral preparations. In some embodiments, tablets can be coated by standard aqueous or nonaqueous techniques.

Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as *acacia*, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, microcrystalline cellulose, and mixtures thereof.

Examples of suitable fillers for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pregelatinized starch, and mixtures thereof.

Disintegrants can be used in the pharmaceutical compositions as provided herein to provide tablets that disintegrate when exposed to an aqueous environment. Too much of a disintegrant can produce tablets which can disintegrate in the bottle. Too little can be insufficient for disintegration to occur and can thus alter the rate and extent of release of the active ingredient(s) from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the active ingredient(s) can be used to form the dosage forms of the compounds disclosed herein. The amount of disintegrant used can vary based upon the type of formulation and mode of administration, and can be readily discernible to those of ordinary skill in the art. About 0.5 to about 15 weight percent of disintegrant, or about 1 to about 5 weight percent of disintegrant, can be used in the pharmaceutical composition. Disintegrants that can be used to form pharmaceutical compositions and dosage forms include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums or mixtures thereof.

Lubricants which can be used to form pharmaceutical compositions and dosage forms include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethylaureate, agar, or mixtures thereof. Additional lubricants include, for example, a syloid silica gel, a coagulated aerosol of synthetic silica, or mixtures thereof. A lubricant can optionally be added, in an amount of less than about 1 weight percent of the pharmaceutical composition.

When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient therein can be combined with various sweetening or flavoring agents, coloring matter or dyes and, for example, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

The tablets can be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

Surfactant which can be used to form pharmaceutical compositions and dosage forms include, but are not limited to, hydrophilic surfactants, lipophilic surfactants, and mixtures thereof. That is, a mixture of hydrophilic surfactants can be employed, a mixture of lipophilic surfactants can be employed, or a mixture of at least one hydrophilic surfactant and at least one lipophilic surfactant can be employed.

A suitable hydrophilic surfactant can generally have an HLB value of at least about 10, while suitable lipophilic surfactants can generally have an HLB value of or less than about 10. An empirical parameter used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance ("HLB" value). Surfactants with lower HLB values are more lipophilic or hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions. Hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, lipophilic (i.e., hydrophobic) surfactants are compounds having an HLB value equal to or less than about 10. However, HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions.

Hydrophilic surfactants can be either ionic or non-ionic. Suitable ionic surfactants include, but are not limited to, alkylammonium salts; fusidic acid salts; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; lecithins and hydrogenated lecithins; lysolecithins and hydrogenated lysolecithins; phospholipids and derivatives thereof; lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

Within the aforementioned group, ionic surfactants include, by way of example: lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tar-

taric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

Ionic surfactants can be the ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholylsarcosine, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

Hydrophilic non-ionic surfactants can include, but are not limited to, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyalkylene alkyl ethers such as polyethylene glycol alkyl ethers; polyoxyalkylene alkylphenols such as polyethylene glycol alkyl phenols; polyoxyalkylene alkyl phenol fatty acid esters such as polyethylene glycol fatty acids monoesters and polyethylene glycol fatty acids diesters; polyethylene glycol glycerol fatty acid esters; polyglycerol fatty acid esters; polyoxyalkylene sorbitan fatty acid esters such as polyethylene glycol sorbitan fatty acid esters; hydrophilic transesterification products of a polyol with at least one member of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids, and sterols; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylated vitamins and derivatives thereof; polyoxyethylene-polyoxypropylene block copolymers; and mixtures thereof; polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of triglycerides, vegetable oils, and hydrogenated vegetable oils. The polyol can be glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide.

Other hydrophilic-non-ionic surfactants include, without limitation, PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10 oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, and poloxamers.

Suitable lipophilic surfactants include, by way of example only: fatty alcohols; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; propylene glycol fatty acid esters; sorbitan fatty acid esters; polyethylene glycol sorbitan fatty acid esters; sterols and sterol derivatives; polyoxyethylated sterols and sterol derivatives; polyethylene glycol alkyl ethers; sugar esters; sugar ethers; lactic acid derivatives of mono- and di-glycerides; hydrophobic transesterification products of a polyol with at least one member of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols; oil-soluble vitamins/vitamin derivatives; and mixtures thereof. Within this group, non-limiting examples of lipophilic surfactants include glycerol fatty acid esters, propylene glycol fatty acid esters, and mixtures thereof, or are hydrophobic transesterification products of a polyol with at least one member of vegetable oils, hydrogenated vegetable oils, and triglycerides.

In one embodiment, the pharmaceutical composition can include a solubilizer to ensure good solubilization and/or dissolution of a compound as provided herein and to minimize precipitation of the compound. This can be especially important for pharmaceutical compositions for non-oral use, e.g., pharmaceutical compositions for injection. A solubilizer can also be added to increase the solubility of the hydrophilic drug and/or other components, such as surfactants, or to maintain the pharmaceutical composition as a stable or homogeneous solution or dispersion.

Examples of suitable solubilizers include, but are not limited to, the following: alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcutol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives; ethers of polyethylene glycols having an average molecular weight of about 200 to about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofurol) or methoxy PEG; amides and other nitrogen-containing compounds such as 2-pyrrolidone, 2-piperidone, ϵ-caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide and polyvinylpyrrolidone; esters such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, ϵ-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof; and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide, N-methyl pyrrolidones, monooctanoin, diethylene glycol monoethyl ether, and water.

Mixtures of solubilizers can also be used. Examples include, but not limited to, triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-100, glycofurol, transcutol, propylene glycol, and dimethyl isosorbide. In some embodiments, solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol and propylene glycol.

The amount of solubilizer that can be included is not particularly limited. The amount of a given solubilizer can be limited to a bioacceptable amount, which can be readily determined by one of skill in the art. In some circumstances, it can be advantageous to include amounts of solubilizers far in excess of bioacceptable amounts, for example to maximize the concentration of the drug, with excess solubilizer removed prior to providing the pharmaceutical composition to a subject using conventional techniques, such as distillation or evaporation. Thus, if present, the solubilizer can be in a

weight ratio of about 10%, 25%, 50%, 100%, or up to about 200% by weight, based on the combined weight of the drug, and other excipients. If desired, very small amounts of solubilizer can also be used, such as about 5%, 2%, 1% or even less. Typically, the solubilizer can be present in an amount of about 1% to about 100%, more typically about 5% to about 25% by weight.

The pharmaceutical composition can further include one or more pharmaceutically acceptable additives and excipients. Such additives and excipients include, without limitation, detackifiers, anti-foaming agents, buffering agents, polymers, antioxidants, preservatives, chelating agents, viscomodulators, tonicifiers, flavorants, colorants, oils, odorants, opacifiers, suspending agents, binders, fillers, plasticizers, lubricants, and mixtures thereof.

Exemplary preservatives can include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives. Exemplary antioxidants include, but are not limited to, alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite. Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA), citric acid monohydrate, disodium edetate, dipotassium edetate, edetic acid, fumaric acid, malic acid, phosphoric acid, sodium edetate, tartaric acid, and trisodium edetate. Exemplary antimicrobial preservatives include, but are not limited to, benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal. Exemplary antifungal preservatives include, but are not limited to, butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid. Exemplary alcohol preservatives include, but are not limited to, ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol. Exemplary acidic preservatives include, but are not limited to, vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid. Other preservatives include, but are not limited to, tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl. In certain embodiments, the preservative is an anti-oxidant. In other embodiments, the preservative is a chelating agent.

Exemplary oils include, but are not limited to, almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and combinations thereof.

In addition, an acid or a base can be incorporated into the pharmaceutical composition to facilitate processing, to enhance stability, or for other reasons. Examples of pharmaceutically acceptable bases include amino acids, amino acid esters, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrocalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, trimethylamine, tris(hydroxymethyl)aminomethane (TRIS) and the like. Also suitable are bases that are salts of a pharmaceutically acceptable acid, such as acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and the like. Salts of polyprotic acids, such as sodium phosphate, disodium hydrogen phosphate, and sodium dihydrogen phosphate can also be used. When the base is a salt, the cation can be any convenient and pharmaceutically acceptable cation, such as ammonium, alkali metals, alkaline earth metals, and the like. Examples can include, but not limited to, sodium, potassium, lithium, magnesium, calcium and ammonium.

Suitable acids are pharmaceutically acceptable organic or inorganic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, boric acid, phosphoric acid, and the like. Examples of suitable organic acids include acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acids, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid and the like.

1B. Formulations for Parenteral Administration

In some embodiments, provided herein are pharmaceutical compositions for parenteral administration containing a compound as disclosed herein, and a pharmaceutical excipient suitable for parenteral administration. In some embodiments, provided herein are pharmaceutical compositions for parenteral administration containing: (i) an effective amount of a disclosed compound; optionally (ii) an effective amount of one or more second agents; and (iii) one or more pharmaceutical excipients suitable for parenteral administration. In some embodiments, the pharmaceutical composition further contains: (iv) an effective amount of a third agent.

The forms in which the disclosed pharmaceutical compositions can be incorporated for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as

elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, and the like (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils can also be employed.

Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, and the like (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils can also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, for the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like.

Sterile injectable solutions are prepared by incorporating a compound as disclosed herein in the required amount in the appropriate solvent with various other ingredients as enumerated above, as appropriate, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the appropriate other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, certain methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional ingredient from a previously sterile-filtered solution thereof.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use. Injectable compositions can contain from about 0.1 to about 5% w/w of a compound as disclosed herein.

1C. Formulations for Topical Administration

In some embodiments, provided herein are pharmaceutical compositions for topical (e.g., transdermal) administration containing a compound as disclosed herein, and a pharmaceutical excipient suitable for topical administration. In some embodiments, provided herein are pharmaceutical compositions for topical administration containing: (i) an effective amount of a disclosed compound; optionally (ii) an effective amount of one or more second agents; and (iii) one or more pharmaceutical excipients suitable for topical administration. In some embodiments, the pharmaceutical composition further contains: (iv) an effective amount of a third agent.

Pharmaceutical compositions provided herein can be formulated into preparations in solid, semi-solid, or liquid forms suitable for local or topical administration, such as gels, water soluble jellies, creams, lotions, suspensions, foams, powders, slurries, ointments, solutions, oils, pastes, suppositories, sprays, emulsions, saline solutions, dimethylsulfoxide (DMSO)-based solutions. In general, carriers with higher densities are capable of providing an area with a prolonged exposure to the active ingredients. In contrast, a solution formulation can provide more immediate exposure of the active ingredient to the chosen area.

The pharmaceutical compositions also can comprise suitable solid or gel phase carriers or excipients, which are compounds that allow increased penetration of, or assist in the delivery of, therapeutic molecules across the stratum corneum permeability barrier of the skin. There are many of these penetration-enhancing molecules known to those trained in the art of topical formulation. Examples of such carriers and excipients include, but are not limited to, humectants (e.g., urea), glycols (e.g., propylene glycol), alcohols (e.g., ethanol), fatty acids (e.g., oleic acid), surfactants (e.g., isopropyl myristate and sodium lauryl sulfate), pyrrolidones, glycerol monolaurate, sulfoxides, terpenes (e.g., menthol), amines, amides, alkanes, alkanols, water, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Another exemplary formulation for use in the disclosed methods employs transdermal delivery devices ("patches"). Such transdermal patches can be used to provide continuous or discontinuous infusion of a compound as provided herein in controlled amounts, either with or without another agent.

The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Pat. Nos. 5,023,252, 4,992,445 and 5,001,139. Such patches can be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Suitable devices for use in delivering intradermal pharmaceutically acceptable compositions described herein include short needle devices such as those described in U.S. Pat. Nos. 4,886,499; 5,190,521; 5,328,483; 5,527,288; 4,270,537; 5,015,235; 5,141,496; and 5,417,662. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin, such as those described in PCT publication WO 99/34850 and functional equivalents thereof. Jet injection devices which deliver liquid vaccines to the dermis via a liquid jet injector and/or via a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Jet injection devices are described, for example, in U.S. Pat. Nos. 5,480,381; 5,599,302; 5,334,144; 5,993,412; 5,649,912; 5,569,189; 5,704,911; 5,383,851; 5,893,397; 5,466,220; 5,339,163; 5,312,335; 5,503,627; 5,064,413; 5,520,639; 4,596,556; 4,790,824; 4,941,880; 4,940,460; and PCT publications WO 97/37705 and WO 97/13537. Ballistic powder/particle delivery devices which use compressed gas to accelerate vaccine in powder form through the outer layers of the skin to the dermis are suitable. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration.

Topically-administrable formulations can, for example, comprise from about 1% to about 10% (w/w) of a compound provided herein relative to the total weight of the formulation, although the concentration of the compound provided herein in the formulation can be as high as the solubility limit of the compound in the solvent. In some embodiments, topically-administrable formulations can, for example, comprise from about 1% to about 9% (w/w) of a compound provided herein, such as from about 1% to about 8% (w/w), further such as from about 1% to about 7% (w/w), further such as from about 1% to about 6% (w/w), further such as from about 1% to about 5% (w/w), further such as from about 1% to about 4% (w/w), further such as from about 1% to about 3% (w/w), and further such as from about 1% to about 2% (w/w) of a compound provided herein. Formulations for topical administration can further comprise one or more of the additional pharmaceutically acceptable excipients described herein.

1D. Formulations for Inhalation Administration

In some embodiments, provided herein are pharmaceutical compositions for inhalation administration containing a compound as disclosed herein, and a pharmaceutical excipient suitable for topical administration. In some embodiments, provided herein are pharmaceutical compositions for inhalation administration containing: (i) an effective amount of a disclosed compound; optionally (ii) an effective amount of

one or more second agents; and (iii) one or more pharmaceutical excipients suitable for inhalation administration. In some embodiments, the pharmaceutical composition further contains: (iv) an effective amount of a third agent.

Pharmaceutical compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid pharmaceutical compositions can contain suitable pharmaceutically acceptable excipients as described herein. In some embodiments, the pharmaceutical compositions are administered by the oral or nasal respiratory route for local or systemic effect. Pharmaceutical compositions in pharmaceutically acceptable solvents can be nebulized by use of inert gases. Nebulized solutions can be inhaled directly from the nebulizing device or the nebulizing device can be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder pharmaceutical compositions can be administered, e.g., orally or nasally, from devices that deliver the formulation in an appropriate manner.

1E. Formulations for Ocular Administration

In some embodiments, the disclosure provides a pharmaceutical composition for treating ophthalmic disorders. The pharmaceutical composition can contain an effective amount of a compound as disclosed herein and a pharmaceutical excipient suitable for ocular administration. Pharmaceutical compositions suitable for ocular administration can be presented as discrete dosage forms, such as drops or sprays each containing a predetermined amount of an active ingredient a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Other administration forms include intraocular injection, intravitreal injection, topically, or through the use of a drug eluting device, microcapsule, implant, or microfluidic device. In some cases, the compounds as disclosed herein are administered with a carrier or excipient that increases the intraocular penetrance of the compound such as an oil and water emulsion with colloid particles having an oily core surrounded by an interfacial film. It is contemplated that all local routes to the eye can be used including topical, subconjunctival, periocular, retrobulbar, subtenon, intracameral, intravitreal, intraocular, subretinal, juxtascleral and suprachoroidal administration. Systemic or parenteral administration can be feasible including, but not limited to intravenous, subcutaneous, and oral delivery. An exemplary method of administration will be intravitreal or subtenon injection of solutions or suspensions, or intravitreal or subtenon placement of bioerodible or non-bioerodible devices, or by topical ocular administration of solutions or suspensions, or posterior juxtascleral administration of a gel or cream formulation.

Eye drops can be prepared by dissolving the active ingredient in a sterile aqueous solution such as physiological saline, buffering solution, etc., or by combining powder compositions to be dissolved before use. Other vehicles can be chosen, as is known in the art, including, but not limited to: balance salt solution, saline solution, water soluble polyethers such as polyethyene glycol, polyvinyls, such as polyvinyl alcohol and povidone, cellulose derivatives such as methylcellulose and hydroxypropyl methylcellulose, petroleum derivatives such as mineral oil and white petrolatum, animal fats such as lanolin, polymers of acrylic acid such as carboxypolymethylene gel, vegetable fats such as peanut oil and polysaccharides such as dextrans, and glycosaminoglycans such as sodium hyaluronate. In some embodiments, additives ordinarily used in the eye drops can be added. Such additives include isotonizing agents (e.g., sodium chloride, etc.), buffer agent (e.g., boric acid, sodium monohydrogen phosphate, sodium dihydrogen phosphate, etc.), preservatives (e.g., benzalkonium chloride, benzethonium chloride, chlorobutanol, etc.), thickeners (e.g., saccharide such as lactose, mannitol, maltose, etc.; e.g., hyaluronic acid or its salt such as sodium hyaluronate, potassium hyaluronate, etc.; e.g., mucopolysaccharide such as chondroitin sulfate, etc.; e.g., sodium polyacrylate, carboxyvinyl polymer, crosslinked polyacrylate, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents known to those skilled in the art).

In some cases, the colloid particles include at least one cationic agent and at least one non-ionic surfactant such as a poloxamer, tyloxapol, a polysorbate, a polyoxyethylene castor oil derivative, a sorbitan ester, or a polyoxyl stearate. In some cases, the cationic agent is an alkylamine, a tertiary alkyl amine, a quaternary ammonium compound, a cationic lipid, an amino alcohol, a biguanidine salt, a cationic compound or a mixture thereof. In some cases, the cationic agent is a biguanidine salt such as chlorhexidine, polyaminopropyl biguanidine, phenformin, alkylbiguanidine, or a mixture thereof. In some cases, the quaternary ammonium compound is a benzalkonium halide, lauralkonium halide, cetrimide, hexadecyltrimethylammonium halide, tetradecyltrimethylammonium halide, dodecyltrimethylammonium halide, cetrimonium halide, benzethonium halide, behenalkonium halide, cetalkonium halide, cetethyldimonium halide, cetylpyridinium halide, benzododecinium halide, chlorallyl methenamine halide, rnyristylalkonium halide, stearalkonium halide or a mixture of two or more thereof. In some cases, cationic agent is a benzalkonium chloride, lauralkonium chloride, benzododecinium bromide, benzethenium chloride, hexadecyltrimethylammonium bromide, tetradecyltrimethylammonium bromide, dodecyltrimethylammonium bromide or a mixture of two or more thereof. In some cases, the oil phase is mineral oil and light mineral oil, medium chain triglycerides (MCT), coconut oil; hydrogenated oils comprising hydrogenated cottonseed oil, hydrogenated palm oil, hydrogenate castor oil or hydrogenated soybean oil; polyoxyethylene hydrogenated castor oil derivatives comprising poluoxyl-40 hydrogenated castor oil, polyoxyl-60 hydrogenated castor oil or polyoxyl-100 hydrogenated castor oil.

1F. Formulations for Controlled Release Administration

In some embodiments, provided herein are pharmaceutical compositions for controlled release administration containing a compound as disclosed herein, and a pharmaceutical excipient suitable for controlled release administration. In some embodiments, provided herein are pharmaceutical compositions for controlled release administration containing: (i) an effective amount of a disclosed compound; optionally (ii) an effective amount of one or more second agents; and (iii) one or more pharmaceutical excipients suitable for controlled release administration. In some embodiments, the pharmaceutical composition further contains: (iv) an effective amount of a third agent.

Active agents such as the compounds provided herein can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Pat. Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; 6,699,500 each of which is incorpo-

rated herein by reference. Such dosage forms can be used to provide slow or controlled release of one or more active agents using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active agents provided herein. Thus, the pharmaceutical compositions provided encompass single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled release.

All controlled release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non controlled counterparts. In some embodiments, the use of a controlled release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the disease, disorder, or condition in a minimum amount of time. Advantages of controlled release formulations include extended activity of the drug, reduced dosage frequency, and increased subject compliance. In addition, controlled release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (e.g., adverse) effects.

In some embodiments, controlled release formulations are designed to initially release an amount of a compound as disclosed herein that promptly produces the desired therapeutic effect, and gradually and continually release other amounts of the compound to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of the compound in the body, the compound should be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled release of an active agent can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

In certain embodiments, the pharmaceutical composition can be administered using intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration. In one embodiment, a pump can be used (see, Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald et al., *Surgery* 88:507 (1980); Saudek et al., *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in a subject at an appropriate site determined by a practitioner of skill, e.g., thus requiring only a fraction of the systemic dose (see, e.g., Goodson, *Medical Applications of Controlled Release,* 115-138 (vol. 2, 1984). Other controlled release systems are discussed in the review by Langer, *Science* 249:1527-1533 (1990). The one or more active agents can be dispersed in a solid inner matrix, e.g., polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, e.g., polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The one or more active agents then diffuse through the outer polymeric membrane in a release rate controlling step. The percentage of active agent in such parenteral compositions is highly dependent on the specific nature thereof, as well as the needs of the subject.

2. Dosage

A compound described herein can be delivered in the form of pharmaceutically acceptable compositions which comprise a therapeutically effective amount of one or more compounds described herein and/or one or more additional therapeutic agents such as a chemotherapeutic, formulated together with one or more pharmaceutically acceptable excipients. In some instances, the compound described herein and the additional therapeutic agent are administered in separate pharmaceutical compositions and can (e.g., because of different physical and/or chemical characteristics) be administered by different routes (e.g., one therapeutic is administered orally, while the other is administered intravenously). In other instances, the compound described herein and the additional therapeutic agent can be administered separately, but via the same route (e.g., both orally or both intravenously). In still other instances, the compound described herein and the additional therapeutic agent can be administered in the same pharmaceutical composition.

The selected dosage level will depend upon a variety of factors including, for example, the activity of the particular compound employed, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the rate and extent of absorption, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

In general, a suitable daily dose of a compound described herein and/or a chemotherapeutic will be that amount of the compound which, in some embodiments, can be the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described herein. Generally, doses of the compounds described herein for a patient, when used for the indicated effects, will range from about 0.0001 mg to about 100 mg per day, or about 0.001 mg to about 100 mg per day, or about 0.01 mg to about 100 mg per day, or about 0.1 mg to about 100 mg per day, or about 0.0001 mg to about 500 mg per day, or about 0.001 mg to about 500 mg per day, or about 0.01 mg to 1000 mg, or about 0.01 mg to about 500 mg per day, or about 0.1 mg to about 500 mg per day, or about 1 mg to 50 mg per day, or about 5 mg to 40 mg per day. An exemplary dosage is about 10 to 30 mg per day. In some embodiments, for a 70 kg human, a suitable dose would be about 0.05 to about 7 g/day, such as about 0.05 to about 2.5 g/day. Actual dosage levels of the active ingredients in the pharmaceutical compositions described herein can be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. In some instances, dosage levels below the lower limit of the aforesaid range can be more than adequate, while in other cases still larger doses can

be employed without causing any harmful side effect, e.g., by dividing such larger doses into several small doses for administration throughout the day.

In some embodiments, the compounds can be administered daily, every other day, three times a week, twice a week, weekly, or bi-weekly. The dosing schedule can include a "drug holiday," e.g., the drug can be administered for two weeks on, one week off, or three weeks on, one week off, or four weeks on, one week off, etc., or continuously, without a drug holiday. The compounds can be administered orally, intravenously, intraperitoneally, topically, transdermally, intramuscularly, subcutaneously, intranasally, sublingually, or by any other route.

In some embodiments, a compound as provided herein is administered in multiple doses. Dosing can be about once, twice, three times, four times, five times, six times, or more than six times per day. Dosing can be about once a month, about once every two weeks, about once a week, or about once every other day. In another embodiment, a compound as disclosed herein and another agent are administered together from about once per day to about 6 times per day. In another embodiment, the administration of a compound as provided herein and an agent continues for less than about 7 days. In yet another embodiment, the administration continues for more than about 6 days, about 10 days, about 14 days, about 28 days, about two months, about six months, or about one year. In some cases, continuous dosing is achieved and maintained as long as necessary.

Administration of the pharmaceutical compositions as disclosed herein can continue as long as necessary. In some embodiments, an agent as disclosed herein is administered for more than about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 14, or about 28 days. In some embodiments, an agent as disclosed herein is administered for less than about 28, about 14, about 7, about 6, about 5, about 4, about 3, about 2, or about 1 day. In some embodiments, an agent as disclosed herein is administered chronically on an ongoing basis, e.g., for the treatment of chronic effects.

Since the compounds described herein can be administered in combination with other treatments (such as additional chemotherapeutics, radiation or surgery), the doses of each agent or therapy can be lower than the corresponding dose for single-agent therapy. The dose for single-agent therapy can range from, for example, about 0.0001 to about 200 mg, or about 0.001 to about 100 mg, or about 0.01 to about 100 mg, or about 0.1 to about 100 mg, or about 1 to about 50 mg per kilogram of body weight per day. In some embodiments, the dose is about 1 mg/kg, about 5 mg/kg, about 7.5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 50 mg/kg, about 75 mg/kg, or about 100 mg/kg per day. In some embodiments, the dose is about 1 mg/kg, about 7.5 mg/kg, about 20 mg/kg, or about 50 mg/kg per day.

When a compound provided herein, is administered in a pharmaceutical composition that comprises one or more agents, and the agent has a shorter half-life than the compound provided herein unit dose forms of the agent and the compound provided herein can be adjusted accordingly.

3. Kits

In some embodiments, provided herein are kits. The kits can include a compound or pharmaceutical composition as described herein, in suitable packaging, and written material that can include instructions for use, discussion of clinical studies, listing of side effects, and the like. Such kits can also include information, such as scientific literature references, package insert materials, clinical trial results, and/or summaries of these and the like, which indicate or establish the activities and/or advantages of the pharmaceutical composition, and/or which describe dosing, administration, side effects, drug interactions, or other information useful to the health care provider. Such information can be based on the results of various studies, for example, studies using experimental animals involving in vivo models and studies based on human clinical trials.

In some embodiments, a memory aid is provided with the kit, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, e.g., as follows "First Week, Monday, Tuesday, ... etc. ... Second Week, Monday, Tuesday, ..." etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several tablets or capsules to be taken on a given day.

The kit can further contain another agent. In some embodiments, the compound as disclosed herein and the agent are provided as separate pharmaceutical compositions in separate containers within the kit. In some embodiments, the compound as disclosed herein and the agent are provided as a single pharmaceutical composition within a container in the kit. Suitable packaging and additional articles for use (e.g., measuring cup for liquid preparations, foil wrapping to minimize exposure to air, and the like) are known in the art and can be included in the kit. In other embodiments, kits can further comprise devices that are used to administer the active agents. Examples of such devices include, but are not limited to, syringes, drip bags, patches, and inhalers. Kits described herein can be provided, marketed and/or promoted to health providers, including physicians, nurses, pharmacists, formulary officials, and the like. Kits can also, in some embodiments, be marketed directly to the consumer.

An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process, recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. The strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

Kits can further comprise pharmaceutically acceptable vehicles that can be used to administer one or more active agents. For example, if an active agent is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active agent can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil,

cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

The present disclosure further encompasses anhydrous pharmaceutical compositions and dosage forms comprising an active ingredient, since water can facilitate the degradation of some compounds. For example, water can be added (e.g., about 5%) in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. Anhydrous pharmaceutical compositions and dosage forms can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. For example, pharmaceutical compositions and dosage forms which contain lactose can be made anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected. An anhydrous pharmaceutical composition can be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous pharmaceutical compositions can be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

Therapeutic Methods

Phosphoinositide 3-kinases (PI3Ks) are members of a conserved family of lipid kinases that regulate numerous cell functions, including proliferation, differentiation, cell survival and metabolism. Several classes of PI3Ks exist in mammalian cells, including Class IA subgroup (e.g., PI3K-α, β, δ), which are generally activated by receptor tyrosine kinases (RTKs); Class IB (e.g., PI3K-γ), which is activated by G-protein coupled receptors (GPCRs), among others. PI3Ks exert their biological activities via a "PI3K-mediated signaling pathway" that includes several components that directly and/or indirectly transduce a signal triggered by a PI3K, including the generation of second messenger phophotidylinositol, 3,4,5-triphosphate (PIP3) at the plasma membrane, activation of heterotrimeric G protein signaling, and generation of further second messengers such as cAMP, DAG, and IP3, all of which leads to an extensive cascade of protein kinase activation (reviewed in Vanhaesebroeck, B. et al. (2001) *Annu Rev Biochem.* 70:535-602). For example, PI3K-δ is activated by cellular receptors through interaction between the PI3K regulatory subunit (p85) SH2 domains, or through direct interaction with RAS. PIP3 produced by PI3K activates effector pathways downstream through interaction with plextrin homology (PH) domain containing enzymes (e.g., PDK-1 and AKT [PKB]). (Fung-Leung W P. (2011) *Cell Signal.* 23(4):603-8). Unlike PI3K-δ, PI3K-γ is not associated with a regulatory subunit of the p85 family, but rather with a regulatory subunit in the p101 family. PI3K-γ is associated with GPCRs, and is responsible for the very rapid induction of PIP3. PI3K-γ can be also activated by RAS.

In some embodiments, provided herein are methods of modulating a PI3 kinase activity (e.g., selectively modulating) by contacting the kinase with an effective amount of a compound as provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein. Modulation can be inhibition (e.g., reduction) or activation (e.g., enhancement) of kinase activity. In some embodiments, provided herein are methods of inhibiting kinase activity by contacting the kinase with an effective amount of a compound as provided herein in solution. In some embodiments, provided herein are methods of inhibiting the kinase activity by contacting a cell, tissue, organ that express the kinase of interest, with a compound provided herein. In some embodiments, provided herein are methods of inhibiting kinase activity in a subject by administering into the subject an effective amount of a compound as provided herein, or a pharmaceutically acceptable form thereof. In some embodiments, the kinase activity is inhibited (e.g., reduced) by more than about 25%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%, when contacted with a compound provided herein as compared to the kinase activity without such contact. In some embodiments, provided herein are methods of inhibiting PI3 kinase activity in a subject (including mammals such as humans) by contacting said subject with an amount of a compound as provided herein sufficient to inhibit or reduce the activity of the PI3 kinase in said subject.

In some embodiments, the kinase is a lipid kinase or a protein kinase. In some embodiments, the kinase is selected from a PI3 kinase including different isoforms, such as PI3 kinase α, PI3 kinase β, PI3 kinase γ, PI3 kinase δ; DNA-PK; mTOR; Abl, VEGFR, Ephrin receptor B4 (EphB4); TEK receptor tyrosine kinase (TIE2); FMS-related tyrosine kinase 3 (FLT-3); Platelet derived growth factor receptor (PDGFR); RET; ATM; ATR; hSmg-1; Hck; Src; Epidermal growth factor receptor (EGFR); KIT; Inulsin Receptor (IR); and IGFR.

As used herein, a "PI3K-mediated disorder" refers to a disease or condition involving aberrant PI3K-mediated signaling pathway. In one embodiment, provided herein is a method of treating a PI3K mediated disorder in a subject, the method comprising administering a therapeutically effective amount of a compound as provided herein, or a pharmaceutically acceptable form thereof, or a pharmaceutical composition as provided herein. In some embodiments, provided herein is a method of treating a PI3K-δ or PI3K-γ mediated disorder in a subject, the method comprising administering a therapeutically effective amount of a compound as provided herein, or a pharmaceutically acceptable form thereof, or a pharmaceutical composition as provided herein. In some embodiments, provided herein is a method for inhibiting at least one of PI3K-δ and PI3K-γ, the method comprising contacting a cell expressing PI3K in vitro or in vivo with an effective amount of a compound or composition provided herein. PI3Ks have been associated with a wide range of conditions, including immunity, cancer and thrombosis (reviewed in Vanhaesebroeck, B. et al. (2010) *Current Topics in Microbiology and Immunology*, DOI 10.1007/82_2010_65). For example, Class I PI3Ks, particularly PI3K-γ and PI3K-δ isoforms, are highly expressed in leukocytes and have been associated with adaptive and innate immunity; thus, these PI3Ks are believed to be important mediators in inflammatory disorders and hematologic malignancies (reviewed in Harris, S J et al. (2009) *Curr Opin Investig Drugs* 10(11):1151-62); Rommel C. et al. (2007) *Nat Rev Immunol* 7(3):191-201; Durand C A et al. (2009) *J. Immunol.* 183(9):5673-84; Dil N, Marshall A J. (2009) *Mol Immunol.* 46(10):1970-8; Al-Alwan M M et al. (2007) *J. Immunol.* 178(4):2328-35; Zhang T T, et al. (2008) *J Allergy Clin Immunol.* 2008; 122(4):811-819.e2; Srinivasan L, et al. (2009) *Cell* 139(3):573-86).

PI3K-γ is a Class 1B PI3K that associates with the p101 and p84 (p87PIKAP) adaptor proteins, and canonically signals through GPCRs. Non-cononical activation through tyrosine kinase receptors and RAS can occur. Activated PI3K-γ leads to production of PIP3, which serves as a docking site for downstream effector proteins including AKT and BTK, bringing these enzymes to the cell membrane where they may be activated. A scaffolding role for PI3k-γ has been proposed and may contribute to the activation of the RAS/MEK/ERK pathway. The interaction with the RAS pathway explains

activities attributed to kinase dead PI3K-γ in cells or in animals. PI3K-γ is essential for function of a variety of immune cells and pathways. Chemokine responses (including IL-8, fMLP, and C5a), leading to neutrophil or monocyte cell migration, is dependent on PI3K-γ (HIRSCH et al., "Central Role for G Protein-Coupled Phosphoinositide 3-Kinase γ in Inflammation," *Science* 287:1049-1053 (2000); SASAKI et al., "Function of PI3Kγ in Thymocyte Development, T Cell Activation, and Neutrophil Migration," *Science* 287:1040-1046 (2000); L I et al., "Roles of PLC-β2 and -β3 and PI3Kγ in Chemoattractant-Mediated Signal Transduction," *Science* 287:1046-1049 (2000)). The requirement for PI3K-γ-dependent neutrophil migration is demonstrated by failure of arthritis development in the K/B×N serum transfer arthritis model in PI3K-γ knockout mice (Randis et al., *Eur. J. Immunol.,* 2008, 38(5), 1215-24). Similarly, the mice fail to develop cellular inflammation and airway hyper-responsiveness in the ovalbumin induced asthma model (Takeda et al., *J. Allergy Clin. Immunol.,* 2009; 123, 805-12). PI3K-γ deficient mice also have defects in T-helper cell function. T-cell cytokine production and proliferation in response to activation is reduced, and T helper dependent viral clearance is defective (Sasaki et al., *Science,* 2000, 287, 1040-46). T cell dependent inflammatory disease models including EAE also do not develop in PI3K-γ deficient mice, and both the T-cell activation defect and cellular migration defects may contribute to efficacy in this model (Comerfold, *PLOS One,* 2012, 7, e45095). The imiquimod psoriasis model has also been used to demonstrate the importance of PI3K-γ in the inflammatory response. Using PI3K-γdeficient mice in this model, the accumulation of γδ T cells in the skin is blocked, as well as dendritic cell maturation and migration (ROLLER et al., "Blockade of Phosphatidylinositol 3-Kinase (PI3K)δ or PI3Kγ Reduces IL-17 and Ameliorates Imiquimod-Induced Psoriasis-like Dermatitis," *J. Immunol.* 189:4612-4620 (2012)). The role of PI3K-γ in cellular trafficking can also be demonstrated in oncology models where tumor inflammation is important for growth and metastasis of cancers. In the Lewis Lung Carcinoma model, monocyte activation, migration, and differentiation in tumors are defective. This defect results in a reduction in tumor growth and extended survival in PI3K-γ deficient mice (Schmid et al., *Cancer Cell,* 2011, 19, 715-27) or upon treatment with inhibitors that target PI3K-γ. In pancreatic cancer, PI3K-γ can be inappropriately expressed, and in this solid tumor cancer or others where PI3K-γ plays a functional role, inhibition of PI3K-γ can be beneficial Inhibition of PI3K-γ shows promise for the treatment of hematologic malignancies. In a T-ALL model employing a T cell directed knockout of P-Ten, PI3K-δ and PI3K-γ are both essential for the appropriate development of disease, as shown with genetic deletion of both genes (Subramaniam et al. *Cancer Cell* 21, 459-472, 2012). In addition, in this TALL model, treatment with a small molecule inhibitor of both kinases leads to extended survival of these mice. In CLL, chemokine networks support a pseudo-follicular microenvironment that includes Nurse like cells, stromal cells and T-helper cells. The roles of PI3K-γ in the normal chemokine signaling and T cell biology suggest the value of inhibiting this target in CLL (BURGER, "Inhibiting B-Cell Receptor Signaling Pathways in Chronic Lymphocytic Leukemia," *Curr. Mematol. Malig. Rep.* 7:26-33 (2012)). Accordingly, PI3K-γ inhibitors are therapeutically interesting for diseases of the immune system where cell trafficking and T cell or myeloid cell function is important. In oncology, solid tumors that are dependent on tumor inflammation, or tumors with high levels of PI3K-γ expression, can be targeted. For hematological cancers a special role for PI3K-γ and PI3K-δ isoforms in TALL and potentially in CLL suggests targeting these PI3Ks in these diseases.

Without being limited by a particular theory, PI3K-γ has been shown to play roles in inflammation, arthritis, asthma, allergy, multiple sclerosis (MS), and cancer, among others (e.g., Ruckle et al., *Nature Rev., Drug Discovery,* 2006, 5, 903-18; Schmid et al., "Myeloid cells in tumor inflammation, " *Vascular Cell,* 2012, doi:10.1186/2045-824X-4-14). For example, PI3K-γ functions in multiple signaling pathways involved in leukocyte activation and migration. PI3K-γ has been shown to drive priming and survival of autoreactive $CD4^+$ T cells during experimental autoimmune encephalomyelitis (EAE), a model for MS. When administered from onset of EAE, a PI3K-γ inhibitor has been shown to cause inhibition and reversal of clinical disease, and reduction of demyelination and cellular pathology in the CNS (Comerford et al., *PLOS One,* 2012, 7, e45095). PI3K-γ also regulates thymocyte development, T cell activation, neutrophil migration, and the oxidative burst (Sasaki et al., *Science,* 2000, 287, 1040-46). In addition, it is shown that allergic airway hyperresponsiveness, inflammation, and remodeling do not develop in PI3K-γ deficient mice (Takeda et al., *J. Allergy Clin. Immunol.,* 2009; 123, 805-12). PI3K-γ is shown to be required for chemoattractant-induced production of phosphatidylinositol 3,4,5-trisphosphate and has an important role in chemoattractant-induced superoxide production and chemotaxis in mouse neutrophils and in production of T cell-independent antigen-specific antibodies composed of the immunoglobulin λ light chain (Li et al., *Science,* 2000, 287, 1046-49). PI3K-γ is reported to be a crucial signaling molecule required for macrophage accumulation in inflammation (Hirsch et al., *Science,* 2000, 287, 1049-53). In cancers, pharmacological or genetic blockade of p110γ suppresses inflammation, growth, and metastasis of implanted and spontaneous tumors, suggesting that PI3K-γ can be an important therapeutic target in oncology (Schmid et al., *Cancer Cell,* 2011, 19, 715-27). For example, it is shown that PI3K-γ has a tumor-specific high accumulation in pancreatic ductal adenocarcinoma (PDAC) in human, signifying a role of PI3K-γ in pancreatic cancer (Edling et al., *Human Cancer Biology,* 2010, 16(2), 4928-37).

PI3K-δ has roles in impairments of B-cell signaling and development, antibody production, T-cell function, Th1 and Th2 differentiation, and mast and basophil degranulation. Without being limited by a particular theory, PI3K-γ has roles in T-cell function, neutrophil and macrophage recruitment, macrophage activation, neutrophil oxidative burst, and dendritic cell migration. Inhibition of PI3K-δ and/or PI3K-γ isoforms can result in efficacy against inflammation and cancer, e.g., in arthritis, asthma, multiple sclerosis (MS), and tumor models. For example, deficiency in PI3K-δ and/or PI3K-γ can result in efficacy in K/B×N arthritis model (Kyburz et al., *Springer Semin. Immunopathology,* 2003, 25, 79-90) or K/B×N serum transfer model of arthritis (Randis et al., *Eur. J. Immunol.,* 2008, 38(5), 1215-24), where it is shown that recognition of the immune complexes depends on both PI3K-δ and PI3K-γ, whereas cell migration is dependent on PI3K-γ. Deficiency in PI3K-δ or PI3K-γ can also result in efficacy in murine ovalbumin (OVA) induced allergic asthma model (Lee et al., *FASEB J.,* 2006, 20, 455-65; Takeda et al., *J. Allergy Clin. Immunol.,* 2009; 123, 805-12), where it is shown that inhibition of either PI3K-δ or PI3K-γ inhibits ovalbumin induced lung infiltration and improves airway responsiveness. Deficiency in PI3K-δ or PI3K-γ can also result in efficacy in murine experimental autoimmune encephalomyelitis (model for MS), where it is shown that PI3K-γ deletion may provide better efficacy as compared to PI3K-δ deletion (Hay-

lock-Jacob et al., *J. Autoimmunity,* 2011, 36, 278-87; Comerford et al., *PLOS One,* 2012, 7, e45095), including reduction in T-cell receptor induced $CD4^+$ T cell activation, leukocyte infiltration and Th1/Th17 responses, and dendritic cell migration (Comerfold, *PLOS One,* 2012, 7, e45095). Furthermore, inhibition of PI3K-γ can also result in decreased tumor inflammation and growth (e.g., Lewis lung carcinoma model, Schmid et al., *Cancer Cell,* 2011, 19(6), 715-27). PI3K-γ deletion combined with PI3K-δ deletion results in increased survival in T-cell acute lymphoblastic leukemia (T-ALL) (Subramaniam et al., *Cancer Cell,* 2012, 21, 459-72) Inhibitors of both PI3K-δ and PI3K-γ are also shown to be efficacious in PTEN-deleted T-ALL cell line (MOLT-4). In the absence of PTEN phosphatase tumor suppressor function, PI3K-δ or PI3K-γ alone can support the development of leukemia, whereas inactivation of both isoforms suppresses tumor formation. Thus, inhibitors of PI3K-δ and/or PI3K-γ can be useful in treating inflammation, such as arthritis, allergic asthma, and MS; and in treating cancer, for example, due to effects such as reductions in solid tumor associated inflammation, angiogenesis and tumor progression.

The importance of PI3K-δ in the development and function of B-cells is supported from inhibitor studies and genetic models. PI3K-δ is an important mediator of B-cell receptor (BCR) signaling, and is upstream of AKT, calcium flux, PLCγ, MAP kinase, P70S6k, and FOXO3a activation. PI3K-δ is also important in IL4R, S1P, and CXCR5 signaling, and has been shown to modulate responses to toll-like receptors 4 and 9 Inhibitors of PI3K-δ have shown the importance of PI3K-δ in B-cell development (Marginal zone and B1 cells), B-cell activation, chemotaxis, migration and homing to lymphoid tissue, and in the control of immunoglobulin class switching leading to the production of IgE. Clayton E et al. (2002) *J Exp Med.* 196(6):753-63; Bilancio A, et al. (2006) *Blood* 107(2):642-50; Okkenhaug K. et al. (2002) *Science* 297(5583):1031-4; Al-Alwan M M et al. (2007) *J Immunol.* 178(4):2328-35; Zhang T T, et al. (2008) *J Allergy Clin Immunol.* 2008; 122(4):811-819.e2; Srinivasan L, et al. (2009) *Cell* 139(3):573-86).

In T-cells, PI3K-δ has been demonstrated to have a role in T-cell receptor and cytokine signaling, and is upstream of AKT, PLCγ, and GSK3b. In PI3K-δ deletion or kinase-dead knock-in mice, or in inhibitor studies, T-cell defects including proliferation, activation, and differentiation have been observed, leading to reduced T helper cell 2 (TH2) response, memory T-cell specific defects (DTH reduction), defects in antigen dependent cellular trafficking, and defects in chemotaxis/migration to chemokines (e.g., SIP, CCR7, CD62L). (Garçon F. et al. (2008) *Blood* 111(3):1464-71; Okkenhaug K et al. (2006). J. Immunol. 177(8):5122-8; Soond D R, et al. (2010) *Blood* 115(11):2203-13; Reif K, (2004). *J Immunol* 2004; 173(4):2236-40; Ji H. et al. (2007) *Blood* 110(8):2940-7; Webb L M, et al. (2005) *J Immunol.* 175(5):2783-7; Liu D, et al. (2010) *J Immunol.* 184(6):3098-105; Haylock-Jacobs S, et al. (2011) *J Autoimmun.* 2011; 36(3-4):278-87; Jarmin S J, et al. (2008) *J Clin Invest.* 118(3):1154-64).

Numerous publications support roles of PI3K-δ and PI3K-γ in the differentiation, maintenance, and activation of immune and malignant cells, as described in more detail herein.

PI3K-δ and PI3K-γ isoforms are preferentially expressed in leukocytes where they have distinct and non-overlapping roles in immune cell development and function. See, e.g., PURI and GOLD, "Selective inhibitors of phosphoinositide 3-kinase delta: modulators of B-cell function with potential for treating autoimmune inflammatory disease and B-cell malignancies," *Front. Immunol.* 3:256 (2012); BUITENHUIS et al., "The role of the PI3k-PKB signaling module in regulation of hematopoiesis," *Cell Cycle* 8(4):560-566 (2009); HOELLENRIEGEL and BURGER, "Phosphoinositide 3'-kinase delta: turning off BCR signaling in Chronic Lymphocytic Leukemia," *Oncotarget* 2(10):737-738 (2011); HIRSCH et al., "Central Role for G Protein-Coupled Phosphoinositide 3-Kinase γ in Inflammation," *Science* 287:1049-1053 (2000); L I et al., "Roles of PLC-β2 and -β3 and PI3Kγ in Chemoattractant-Mediated Signal Transduction," *Science* 287:1046-1049 (2000); SASAKI et al., "Function of PI3Kγ in Thymocyte Development, T Cell Activation, and Neutrophil Migration," *Science* 287:1040-1046 (2000); CUSHING et al., "PI3Kδ and PI3Kγ as Targets for Autoimmune and Inflammatory Diseases," *J. Med. Chem.* 55:8559-8581 (2012); MAXWELL et al., "Attenuation of phosphoinositide 3-kinase δ signaling restrains autoimmune disease," *J. Autoimmun.* 38:381-391 (2012); HAYLOCK-JACOBS et al., "PI3Kδ drives the pathogenesis of experimental autoimmune encephalomyelitis by inhibiting effector T cell apoptosis and promoting Th17 differentiation," *J. Autoimmun.* 36:278-287 (2011); SOOND et al., "PI3K p110δ regulates T-cell cytokine production during primary and secondary immune responses in mice and humans," *Blood* 115(11):2203-2213 (2010); ROLLER et al., "Blockade of Phosphatidylinositol 3-Kinase (PI3K)δ or PI3Kγ Reduces IL-17 and Ameliorates Imiquimod-Induced Psoriasis-like Dermatitis," *J. Immunol.* 189: 4612-4620 (2012); CAMPS et al., "Blockade of PI3Kγ suppresses joint inflammation and damage in mouse models of rheumatoid arthritis," *Nat. Med.* 11(9):936-943 (2005). As key enzymes in leukocyte signaling, PI3K-δ and PI3K-γ facilitate normal B-cell, T-cell and myeloid cell functions including differentiation, activation, and migration. See, e.g., HOELLENRIEGEL and BURGER, "Phosphoinositide 3'-kinase delta: turning off BCR signaling in Chronic Lymphocytic Leukemia," *Oncotarget* 2(10):737-738 (2011); CUSHING et al., "PI3Kδ and PI3Kγ as Targets for Autoimmune and Inflammatory Diseases," *J. Med. Chem.* 55:8559-8581 (2012). PI3K-δ or PI3K-γ activity is critical for preclinical models of autoimmune and inflammatory diseases. See, e.g., HIRSCH et al., "Central Role for G Protein-Coupled Phosphoinositide 3-Kinase γ in Inflammation," *Science* 287:1049-1053 (2000); L I et al., "Roles of PLC-β2 and -β3 and PI3Kγ in Chemoattractant-Mediated Signal Transduction," *Science* 287:1046-1049 (2000); SASAKI et al., "Function of PI3Kγ in Thymocyte Development, T Cell Activation, and Neutrophil Migration," *Science* 287:1040-1046 (2000); CUSHING et al., "PI3Kδ and PI3Kγ as Targets for Autoimmune and Inflammatory Diseases," *J. Med. Chem.* 55:8559-8581 (2012); MAXWELL et al., "Attenuation of phosphoinositide 3-kinase δ signaling restrains autoimmune disease," *J. Autoimmun.* 38:381-391 (2012); HAYLOCK-JACOBS et al., "PI3Kδ drives the pathogenesis of experimental autoimmune encephalomyelitis by inhibiting effector T cell apoptosis and promoting Th17 differentiation," *J. Autoimmun.* 36:278-287 (2011); SOOND et al., "PI3K p110δ regulates T-cell cytokine production during primary and secondary immune responses in mice and humans," *Blood* 115(11):2203-2213 (2010); ROLLER et al., "Blockade of Phosphatidylinositol 3-Kinase (PI3K)δ or PI3Kγ Reduces IL-17 and Ameliorates Imiquimod-Induced Psoriasis-like Dermatitis," *J. Immunol.* 189: 4612-4620 (2012); CAMPS et al., "Blockade of PI3Kγ suppresses joint inflammation and damage in mouse models of rheumatoid arthritis," *Nat. Med.* 11(9):936-943 (2005). Given the key role for PI3K-δ and PI3K-γ in immune function, inhibitors of the PI3K-6 and/or γ have therapeutic potential in immune-related inflammatory or neoplastic diseases.

PI3K-δ and PI3K-γ are central to the growth and survival of B- and T-cell malignancies and inhibition of these isoforms may effectively limit these diseases. See, e.g., SUBRAMANIAM et al., "Targeting Nonclassical Oncogenes for Therapy in T-ALL," *Cancer Cell* 21:459-472 (2012); LANNUTTI et al., "CAL-101 a p110δ selective phosphatidylinositol-3-kinase inhibitor for the treatment of B-cell malignancies, inhibits PI3K signaling and cellular viability," *Blood* 117(2):591-594 (2011). PI3K-δ and PI3K-γ support the growth and survival of certain B-cell malignancies by mediating intracellular BCR signaling and interactions between the tumor cells and their microenvironment. See, e.g., PURI and GOLD, "Selective inhibitors of phosphoinositide 3-kinase delta: modulators of B-cell function with potential for treating autoimmune inflammatory disease and B-cell malignancies," *Front. Immunol.* 3:256 (2012); HOELLENRIEGEL et al., "The phosphoinositide 3'-kinase delta inhibitor, CAL-101, inhibits B-cell receptor signaling and chemokine networks in chronic lymphocytic leuckemia," *Blood* 118(13): 3603-3612 (2011); BURGER, "Inhibiting B-Cell Receptor Signaling Pathways in Chronic Lymphocytic Leukemia," Curr. *Mematol. Malig. Rep.* 7:26-33 (2012). Increased BCR signaling is a central pathologic mechanism of B-cell malignancies and PI3K activation is a direct consequence of BCR pathway activation. See, e.g., BURGER, "Inhibiting B-Cell Receptor Signaling Pathways in Chronic Lymphocytic Leukemia," Curr. *Mematol. Malig. Rep.* 7:26-33 (2012); HERISHANU et al., "The lymph node microenvironment promotes B-cell receptor signaling, NF-κB activation, and tumor proliferation in chronic lymphocytic leukemia," *Blood* 117 (2):563-574 (2011); DAVIS et al., "Chronic active B-cell-receptor signaling in diffuse large B-cell lymphoma," *Nature* 463:88-92 (2010); PIGHI et al., "Phospho-proteomic analysis of mantle cell lymphoma cells suggests a pro-survival role of B-cell receptor signaling," *Cell Oncol.* (*Dordr*) 34(2):141-153 (2011); RIZZATTI et al., "Gene expression profiling of mantle cell lymphoma cells reveals aberrant expression of genes from the PI3K-AKT, WNT and TGFβ signaling pathways," *Brit. J. Haematol.* 130:516-526 (2005); MARTINEZ et al., "The Molecular Signature of Mantle Cell Lymphoma Reveals Multiple Signals Favoring Cell Survival," *Cancer Res.* 63:8226-8232 (2003). Interactions between malignant B-cells and supporting cells (eg, stromal cells, nurse-like cells) in the tumor microenvironment are important for tumor cell survival, proliferation, homing, and tissue retention. See, e.g., BURGER, "Inhibiting B-Cell Receptor Signaling Pathways in Chronic Lymphocytic Leukemia," *Curr. Mematol. Malig. Rep.* 7:26-33 (2012); HERISHANU et al., "The lymph node microenvironment promotes B-cell receptor signaling, NF-κB activation, and tumor proliferation in chronic lymphocytic leukemia," *Blood* 117(2):563-574 (2011); KURTOVA et al., "Diverse marrow stromal cells protect CLL cells from spontaneous and drug-induced apoptosis: development of a reliable and reproducible system to assess stromal cell adhesion-mediated drug resistance," *Blood* 114(20): 4441-4450 (2009); BURGER et al., "High-level expression of the T-cell chemokines CCL3 and CCL4 by chronic lymphocytic leukemia B cells in nurselike cell cocultures and after BCR stimulation," *Blood* 113(13) 3050-3058 (2009); QUIROGA et al., "B-cell antigen receptor signaling enhances chronic lymphocytic leukemia cell migration and survival: specific targeting with a novel spleen tyrosine kinase inhibitor, R406," *Blood* 114(5):1029-1037 (2009) Inhibiting PI3K-δ,γ with an inhibitor in certain malignant B-cells can block the BCR-mediated intracellular survival signaling as well as key interactions with their microenvironment that are critical for their growth.

PI3K-δ and PI3K-γ also play a direct role in the survival and proliferation of certain T-cell malignancies. See, e.g., SUBRAMANIAM et al., "Targeting Nonclassical Oncogenes for Therapy in T-ALL," *Cancer Cell* 21:459-472 (2012). Aberrant PI3K-δ and PI3K-γ activity provides the signals necessary for the development and growth of certain T-cell malignancies. While BTK is expressed in B-cells, it is not expressed in T-cells, and therefore BTK is not a viable target for the treatment of T-cell malignancies. See, e.g., NISITANI et al., "Posttranscriptional regulation of Bruton's tyrosine kinase expression in antigen receptor-stimulated splenic B cells," *PNAS* 97(6):2737-2742 (2000); DE WEERS et al., "The Bruton's tyrosine kinase gene is expressed throughout B cell differentiation, from early precursor B cell stages preceding immunoglobulin gene rearrangement up to mature B cell stages," *Eur. J. Immunol.* 23:3109-3114 (1993); SMITH et al., "Expression of Bruton's Agammaglobulinemia Tyrosine Kinase Gene, BTK, Is Selectively Down-Regulated in T Lymphocytes and Plasma Cells," *J. Immunol.* 152: 557-565 (1994). PI3K-δ and/or γ inhibitors may have unique therapeutic potential in T-cell malignancies.

In neutrophils, PI3K-δ, along with PI3K-γ, contribute to the responses to immune complexes, FCγRII signaling, including migration and neutrophil respiratory burst. Human neutrophils undergo rapid induction of PIP3 in response to formyl peptide receptor (FMLP) or complement component C5a (C5a) in a PI3K-γ dependent manner, followed by a longer PIP3 production period that is PI3K-δ dependent, and is essential for respiratory burst. The response to immune complexes is contributed by PI3K-δ, PI3K-γ, and PI3K-β, and is an important mediator of tissue damage in models of autoimmune disease (Randis T M et al. (2008) *Eur J Immunol.* 38(5):1215-24; Pinho V, (2007) *J Immunol.* 179(11): 7891-8; Sadhu C. et al. (2003) *J Immunol.* 170(5):2647-54; Condliffe A M et al. (2005) *Blood* 106(4):1432-40). It has been reported that in certain autoimmune diseases, preferential activation of PI3K-β may be involved (Kulkarni et al., *Immunology* (2011) 4(168) ra23: 1-11). It was also reported that PI3K-β-deficient mice were highly protected in an FcγR-dependent model of autoantibody-induced skin blistering and partially protected in an FcγR-dependent model of inflammatory arthritis, whereas combined deficiency of PI3K-β and PI3K-resulted in near complete protection in inflammatory arthritis (Id.).

In macrophages collected from patients with chronic obstructive pulmonary disease (COPD), glucocorticoid responsiveness can be restored by treatment of the cells with inhibitors of PI3K-δ. Macrophages also rely on PI3K-δ and PI3K-γ for responses to immune complexes through the arthus reaction (FCγR and C5a signaling) (Randis T M, et al. (2008) *Eur J Immunol.* 38(5):1215-24; Marwick J A et al. (2009) *Am J Respir Crit Care Med.* 179(7):542-8; Konrad S, et al. (2008) *J Biol Chem.* 283(48):33296-303).

In mast cells, stem cell factor—(SCF) and IL3-dependent proliferation, differentiation and function are PI3K-δ dependent, as is chemotaxis. The allergen/IgE crosslinking of FCγR1 resulting in cytokine release and degranulation of the mast cells is severely inhibited by treatment with PI3K-δ inhibitors, suggesting a role for PI3K-δ in allergic disease (Ali K et al. (2004) *Nature* 431(7011):1007-11; Lee K S, et al. (2006) *FASEB J.* 20(3):455-65; Kim M S, et al. (2008) *Trends Immunol.* 29(10): 493-501).

Natural killer (NK) cells are dependent on both PI3K-δ and PI3K-γ for efficient migration towards chemokines including CXCL10, CCL3, S1P and CXCL12, or in response to LPS in the peritoneum (Guo H, et al. (2008) *J Exp Med.* 205(10): 2419-35; Tassi I, et al. (2007) *Immunity* 27(2):214-27; Sau-

demont A, (2009) *Proc Natl Acad Sci USA.* 106(14):5795-800; Kim N, et al. (2007) *Blood* 110(9):3202-8).

The roles of PI3K-δ and PI3K-γ in the differentiation, maintenance, and activation of immune cells support a role for these enzymes in inflammatory disorders ranging from autoimmune diseases (e.g., rheumatoid arthritis, multiple sclerosis) to allergic inflammatory disorders, such as asthma, and inflammatory respiratory disease, such as COPD. Extensive evidence is available in experimental animal models, or can be evaluated using art-recognized animal models. In an embodiment, described herein is a method of treating inflammatory disorders ranging from autoimmune diseases (e.g., rheumatoid arthritis, multiple sclerosis) to allergic inflammatory disorders, such as asthma and COPD using a compound described herein.

For example, inhibitors of PI3K-δ and/or -γ have been shown to have anti-inflammatory activity in several autoimmune animal models for rheumatoid arthritis (Williams, O. et al. (2010) Chem Biol, 17(2):123-34; WO 2009/088986; WO2009/088880; WO 2011/008302; each incorporated herein by reference). PI3K-δ is expressed in the RA synovial tissue (especially in the synovial lining which contains fibroblast-like synoviocytes (FLS), and selective PI3K-δ inhibitors have been shown to be effective in inhibiting synoviocyte growth and survival (Bartok et al. (2010) *Arthritis Rheum* 62 Suppl 10:362). Several PI3K-δ and -γ inhibitors have been shown to ameliorate arthritic symptoms (e.g., swelling of joints, reduction of serum-induced collagen levels, reduction of joint pathology and/or inflammation), in art-recognized models for RA, such as collagen-induced arthritis and adjuvant induced arthritis (WO 2009/088986; WO2009/088880; WO 2011/008302; each incorporated herein by reference).

The role of PI3K-δ has also been shown in models of T-cell dependent response, including the DTH model. In the murine experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis, the PI3K-γ/δ-double mutant mice are resistant. PI3K-δ inhibitors have also been shown to block EAE disease induction and development of TH-17 cells both in vitro and in vivo (Haylock-Jacobs, S. et al. (2011) *J. Autoimmunity* 36(3-4):278-87).

Systemic lupus erythematosus (SLE) is a complex disease that at different stages requires memory T-cells, B-cell polyclonal expansion and differentiation into plasma cells, and the innate immune response to endogenous damage associated molecular pattern molecules (DAMPS), and the inflammatory responses to immune complexes through the complement system as well as the F_C receptors. The role of PI3K-δ and PI3K-γ together in these pathways and cell types suggest that blockade with an inhibitor would be effective in these diseases. A role for PI3K in lupus is also predicted by two genetic models of lupus. The deletion of phosphatase and tensin homolog (PTEN) leads to a lupus-like phenotype, as does a transgenic activation of Class 1A PI3Ks, which includes PI3K-δ. The deletion of PI3K-γ in the transgenically activated class 1A lupus model is protective, and treatment with a PI3K-γ selective inhibitor in the murine MLR/lpr model of lupus improves symptoms (Barber, D F et al. (2006) *J. Immunol.* 176(1): 589-93).

In allergic disease, PI3K-δ has been shown by genetic models and by inhibitor treatment to be essential for mast-cell activation in a passive cutaneous anaphalaxis assay (Ali K et al. (2008) *J Immunol.* 180(4): 2538-44; Ali K, (2004) *Nature* 431(7011):1007-11). In a pulmonary measure of response to immune complexes (Arthus reaction) a PI3K-δ knockout is resistant, showing a defect in macrophage activation and C5a production. Knockout studies and studies with inhibitors for both PI3K-δ and PI3K-γ support a role for both of these enzymes in the ovalbumin induced allergic airway inflammation and hyper-responsiveness model (Lee K S et al. (2006) *FASEB J.* 20(3):455-65). Reductions of infiltration of eosinophils, neutrophils, and lymphocytes as well as TH2 cytokines (IL4, IL5, and IL13) were seen with both PI3K-δ specific and dual PI3K-δ and PI3K-γ inhibitors in the Ova induced asthma model (Lee K S et al. (2006) *J Allergy Clin Immunol* 118(2): 403-9).

PI3K-δ and PI3K-γ inhibition can be used in treating COPD. In the smoked mouse model of COPD, the PI3K-δ knockout does not develop smoke induced glucocorticoid resistance, while wild-type and PI3K-γknockout mice do. An inhaled formulation of dual PI3K-δ and PI3K-γ inhibitor blocked inflammation in a LPS or smoke COPD models as measured by neutrophilia and glucocorticoid resistance (Doukas J, et al. (2009) *J Pharmacol Exp Ther.* 328(3):758-65).

Class I PI3Ks, particularly PI3K-δ and PI3K-γ isoforms, are also associated with cancers (reviewed, e.g., in Vogt, P K et al. (2010) Curr Top Microbiol Immunol 347:79-104; Fresno Vara, J A et al. (2004) *Cancer Treat Rev.* 30(2):193-204; Zhao, L and Vogt, P K. (2008) *Oncogene* 27(41):5486-96) Inhibitors of PI3K, e.g., PI3K-δ and/or PI3K-γ, have been shown to have anti-cancer activity (e.g., Courtney, K D et al. (2010) *J Clin Oncol.* 28(6):1075-1083); Markman, B et al. (2010) *Ann Oncol.* 21(4):683-91; Kong, D and Yamori, T (2009) *Curr Med Chem.* 16(22):2839-54; Jimeno, A et al. (2009) *J Clin Oncol.* 27:156s (suppl; abstr 3542); Flinn, I W et al. (2009) *J Clin Oncol.* 27:156s (suppl; abstr 3543); Shapiro, G et al. (2009) *J Clin Oncol.* 27:146s (suppl; abstr 3500); Wagner, A J et al. (2009) *J Clin Oncol.* 27:146s (suppl; abstr 3501); Vogt, P K et al. (2006) *Virology* 344(1):131-8; Ward, S et al. (2003) *Chem Biol.* 10(3):207-13; WO 2011/041399; US 2010/0029693; US 2010/0305096; US 2010/0305084; each incorporated herein by reference).

In one embodiment, described herein is a method of treating cancer. In one embodiment, provided herein is a method of treating a hematological cancer comprising administering a pharmaceutically effective amount of a compound provided herein to a subject in need thereof. In one embodiment, provided herein is a method of treating a solid tumor comprising administering a pharmaceutically effective amount of a compound provided herein to a subject in need thereof. Types of cancer that can be treated with an inhibitor of PI3K (particularly, PI3K-δ and/or PI3K-γ) include, e.g., leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia (e.g., Salmena, L et al. (2008) *Cell* 133: 403-414; Chapuis, N et al. (2010) *Clin Cancer Res.* 16(22): 5424-35; Khwaja, A (2010) *Curr Top Microbiol Immunol.* 347:169-88); lymphoma, e.g., non-Hodgkin's lymphoma (e.g., Salmena, L et al. (2008) *Cell* 133:403-414); lung cancer, e.g., non-small cell lung cancer, small cell lung cancer (e.g., Herrera, V A et al. (2011) *Anticancer Res.* 31(3):849-54); melanoma (e.g., Haluska, F et al. (2007) *Semin Oncol.* 34(6):546-54); prostate cancer (e.g., Sarker, D et al. (2009) *Clin Cancer Res.* 15(15):4799-805); glioblastoma (e.g., Chen, J S et al. (2008) *Mol Cancer Ther.* 7:841-850); endometrial cancer (e.g., Bansal, N et al. (2009) *Cancer Control.* 16(1):8-13); pancreatic cancer (e.g., Furukawa, T (2008) *J Gastroenterol.* 43(12):905-11); renal cell carcinoma (e.g., Porta, C and Figlin, R A (2009) *J Urol.* 182(6):2569-77); colorectal cancer (e.g., Saif, M W and Chu, E (2010) *Cancer J.* 16(3):196-201); breast cancer (e.g., Torbett, N E et al. (2008) *Biochem J.* 415:97-100); thyroid cancer (e.g., Brzezianska, E and Pastuszak-Lewandoska, D (2011) *Front Biosci.* 16:422-39); and ovarian cancer (e.g., Mazzoletti, M and Broggini, M (2010) *Curr Med Chem.* 17(36):4433-47).

Numerous publications support a role of PI3K-δ and PI3K-γ in treating hematological cancers. PI3K-δ and PI3K-γ are highly expressed in the heme compartment, and solid tumors, including prostate, breast and glioblastomas (Chen J. S. et al. (2008) *Mol Cancer Ther.* 7(4):841-50; Ikeda H. et al. (2010) *Blood* 116(9):1460-8).

In hematological cancers including acute myeloid leukemia (AML), multiple myeloma (MM), and chronic lymphocytic leukemia (CLL), overexpression and constitutive activation of PI3K-δ supports the model that PI3K-δ inhibition would be therapeutic Billottet C, et al. (2006) *Oncogene* 25(50):6648-59; Billottet C, et al. (2009) *Cancer Res.* 69(3): 1027-36; Meadows, S A, 52nd Annual ASH Meeting and Exposition; 2010 Dec. 4-7; Orlando, Fla.; Ikeda H, et al. (2010) *Blood* 116(9):1460-8; Herman S E et al. (2010) *Blood* 116(12):2078-88; Herman S E et al. (2011). *Blood* 117(16): 4323-7.

In one embodiment, described herein is a method of treating hematological cancers including, but not limited to acute myeloid leukemia (AML), multiple myeloma (MM), and chronic lymphocytic leukemia (CLL).

A PI3K-δ inhibitor (CAL-101) has been evaluated in a phase 1 trial in patients with haematological malignancies, and showed activity in CLL in patients with poor prognostic characteristics. In CLL, inhibition of PI3K-δ not only affects tumor cells directly, but it also affects the ability of the tumor cells to interact with their microenvironment. This microenvironment includes contact with and factors from stromal cells, T-cells, nurse like cells, as well as other tumor cells. CAL-101 suppresses the expression of stromal and T-cell derived factors including CCL3, CCL4, and CXCL13, as well as the CLL tumor cells' ability to respond to these factors. CAL-101 treatment in CLL patients induces rapid lymph node reduction and redistribution of lymphocytes into the circulation, and affects tonic survival signals through the BCR, leading to reduced cell viability, and an increase in apoptosis. Single agent CAL-101 treatment was also active in mantle cell lymphoma and refractory non Hodgkin's lymphoma (Furman, R R, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec. 4-7; Orlando, Fla.; Hoellenriegel, J, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec. 4-7; Orlando, Fla.; Webb, H K, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec. 4-7; Orlando, Fla.; Meadows, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec. 4-7; Orlando, Fla.; Kahl, B, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec. 4-7; Orlando, Fla.; Lannutti B J, et al. (2011) *Blood* 117(2):591-4).

PI3K-δ inhibitors have shown activity against PI3K-δ positive gliomas in vitro (Kashishian A, et al. Poster presented at: The American Association of Cancer Research 102nd Annual Meeting; 2011 Apr. 2-6; Orlando, Fla.). PI3K-δ is the PI3K isoform that is most commonly activated in tumors where the PTEN tumor suppressor is mutated (Ward S, et al. (2003) *Chem Biol.* 10(3):207-13). In this subset of tumors, treatment with the PI3K-δ inhibitor either alone or in combination with a cytotoxic agent can be effective.

Another mechanism for PI3K-δ inhibitors to have an effect in solid tumors involves the tumor cells' interaction with their micro-environment. PI3K-δ, PI3K-γ, and PI3K-β are expressed in the immune cells that infiltrate tumors, including tumor infiltrating lymphocytes, macrophages, and neutrophils. PI3K-δ inhibitors can modify the function of these tumor-associated immune cells and how they respond to signals from the stroma, the tumor, and each other, and in this way affect tumor cells and metastasis (Hoellenriegel, J, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec. 4-7; Orlando, Fla.).

PI3K-δ is also expressed in endothelial cells. It has been shown that tumors in mice treated with PI3K-δ selective inhibitors are killed more readily by radiation therapy. In this same study, capillary network formation is impaired by the PI3K inhibitor, and it is postulated that this defect contributes to the greater killing with radiation. PI3K-δ inhibitors can affect the way in which tumors interact with their microenvironment, including stromal cells, immune cells, and endothelial cells and be therapeutic either on its own or in conjunction with another therapy (Meadows, S A, et al. Paper presented at: 52nd Annual ASH Meeting and Exposition; 2010 Dec. 4-7; Orlando, Fla.; Geng L, et al. (2004) *Cancer Res.* 64(14):4893-9).

In one embodiment, provided herein is a method of treating or preventing a cancer or disease, such as hematologic malignancy, or a specific type or sub-type of cancer or disease, such as a specific type or sub-type of hematologic malignancy, with a PI3K-γ selective inhibitor, wherein the adverse effects associated with administration of inhibitors for other isoform (s) of PI3K (e.g., PI3K-α and/or PI3K-β) are reduced. In one embodiment, provided herein is a method of treating or preventing a cancer or disease, such as hematologic malignancy, or a specific type or sub-type of cancer or disease, such as a specific type or sub-type of hematologic malignancy, with a PI3K-γ selective inhibitor, at a lower (e.g., by about 10%, by about 20%, by about 30%, by about 40%, by about 50%, by about 60%, by about 70%, or by about 80%) dose as compared to treatment with a PI3K-γ non-selective or less selective PI3K-γ inhibitor (e.g., a PI3Kpan inhibitors, e.g., inhibiting PI3K-α, β, δ, and γ).

The role of PI3K-γ pathway in promoting myeloid cell trafficking to tumors and the role of blockade of p100γ in suppression of tumor inflammation and growth in breast cancer, pancreatic cancer, and lung cancer are reported, for example, in Schmid et al. (2011) *Cancer Cell* 19, 715-727, the entirety of which is incorporated herein by reference. In one embodiment, provided herein is a method of treating or preventing pancreatic cancer with a PI3K inhibitor. In another embodiment, provided herein is a method of treating or preventing breast cancer with a PI3K inhibitor. In yet another embodiment, provided herein is a method of treating or preventing lung cancer with a PI3K inhibitor. In one embodiment, the PI3K inhibitor is a PI3K-γ inhibitor, selective or non-selective over one or more other PI3K isoform(s). In one embodiment, the PI3K inhibitor is a PI3K-γ selective inhibitor.

In certain embodiments, provided herein is a method of treating a disorder or disease provided herein, comprising administering a compound provided herein, e.g., a PI3K γ selective inhibitor, a PI3K δ selective inhibitor, or a PI3K γ/δ dual inhibitor. Without being limited by a particular theory, in some embodiments, selectively inhibiting PI3K-γ isoform can provide a treatment regimen where adverse effects associated with administration of a non-selective PI3K inhibitor are minimized or reduced. Without being limited by a particular theory, in some embodiments, selectively inhibiting PI3K-δ isoform can provide a treatment regimen where adverse effects associated with administration of a non-selective PI3K inhibitor are minimized or reduced. Without being limited by a particular theory, in some embodiments, selectively inhibiting PI3K-δ and γ isoform can provide a treatment regimen where adverse effects associated with administration of a non-selective PI3K inhibitor are minimized or reduced. Without being limited by a particular theory, it is believed that the adverse effects can be reduced by avoiding the inhibition of other isoforms (e.g., α or β) of PI3K.

In one embodiment, the adverse effect is hyperglycemia. In another embodiment, the adverse effect is rash. In another embodiment, the adverse effect is impaired male fertility that may result from inhibition of β isoform of PI3K (see, e.g., Ciraolo et al., *Molecular Biology of the Cell,* 21: 704-711 (2010)). In another embodiment, the adverse effect is testicular toxicity that may result from inhibition of PI3K-β (see, e.g., Wisler et al., Amgen SOT, Abstract ID #2334 (2012)). In another embodiment, the adverse effect is embryonic lethality (see, e.g., Bi et al., *J Biol Chem,* 274: 10963-10968 (1999)). In another embodiment, the adverse effect is defective platelet aggregation (see, e.g., Kulkarni et al., *Science,* 287: 1049-1053 (2000)). In another embodiment, the adverse effect is functionally defective neutrophil (id.).

In certain embodiments, the PI3K-γ inhibitor selectively modulates phosphatidyl inositol-3 kinase (PI3 kinase) gamma isoform. In one embodiment, the PI3K-γ inhibitor selectively inhibits the gamma isoform over the alpha, beta, or delta isoform. In one embodiment, the PI3K-γ inhibitor selectively inhibits the gamma isoform over the alpha or beta isoform. In one embodiment, the PI3K-γ inhibitor selectively inhibits the gamma isoform over the alpha, beta, and delta isoforms. In one embodiment, the PI3K-γ inhibitor selectively inhibits the gamma isoform over the alpha and beta isoforms. In one embodiment, the PI3K-γ inhibitor selectively inhibits the gamma isoform over the alpha and beta isoforms, but not the delta isoform. By way of non-limiting example, the ratio of selectivity can be greater than a factor of about 10, greater than a factor of about 50, greater than a factor of about 100, greater than a factor of about 200, greater than a factor of about 400, greater than a factor of about 600, greater than a factor of about 800, greater than a factor of about 1000, greater than a factor of about 1500, greater than a factor of about 2000, greater than a factor of about 5000, greater than a factor of about 10,000, or greater than a factor of about 20,000, where selectivity can be measured by ratio of IC_{50} values, among other means. In one embodiment, the selectivity of PI3K gamma isoform over an other PI3K isoform is measured by the ratio of the IC_{50} value against the other PI3K isoform to the IC_{50} value against PI3K gamma isoform. In certain embodiments, the PI3 kinase gamma isoform IC_{50} activity of a compound as disclosed herein can be less than about 1000 nM, less than about 100 nM, less than about 10 nM, or less than about 1 nM. For example, a compound that selectively inhibits one isoform of PI3K over another isoform of PI3K has an activity of at least 2× against a first isoform relative to the compound's activity against the second isoform (e.g., at least about 3×, 5×, 10×, 20×, 50×, 100×, 200×, 500×, or 1000×).

In other embodiments, inhibition of PI3K (such as PI3K-δ and/or PI3K-γ) can be used to treat a neuropsychiatric disorder, e.g., an autoimmune brain disorder. Infectious and immune factors have been implicated in the pathogenesis of several neuropsychiatric disorders, including, but not limited to, Sydenham's chorea (SC) (Garvey, M. A. et al. (2005) *J. Child Neurol.* 20:424-429), Tourette's syndrome (TS), obsessive compulsive disorder (OCD) (Asbahr, F. R. et al. (1998) *Am. J. Psychiatry* 155:1122-1124), attention deficit/hyperactivity disorder (AD/HD) (Hirschtritt, M. E. et al. (2008) *Child Neuropsychol.* 1:1-16; Peterson, B. S. et al. (2000) *Arch. Gen. Psychiatry* 57:364-372), anorexia nervosa (Sokol, M. S. (2000) *J. Child Adolesc. Psychopharmacol.* 10:133-145; Sokol, M. S. et al. (2002) *Am. J. Psychiatry* 159:1430-1432), depression (Leslie, D. L. et al. (2008) *J. Am. Acad. Child Adolesc. Psychiatry* 47:1166-1172), and autism spectrum disorders (ASD) (Hollander, E. et al. (1999) *Am. J. Psychiatry* 156:317-320; Margutti, P. et al. (2006) *Curr. Neurovasc. Res.* 3:149-157). A subset of childhood obsessive compulsive disorders and tic disorders has been grouped as Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococci (PANDAS). PANDAS disorders provide an example of disorders where the onset and exacerbation of neuropsychiatric symptoms is preceded by a streptococcal infection (Kurlan, R., Kaplan, E. L. (2004) *Pediatrics* 113: 883-886; Garvey, M. A. et al. (1998) *J. Clin. Neurol.* 13:413-423). Many of the PANDAS disorders share a common mechanism of action resulting from antibody responses against streptococcal associated epitopes, such as GlcNAc, which produces neurological effects (Kirvan. C. A. et al. (2006) *J. Neuroimmunol.* 179:173-179). Autoantibodies recognizing central nervous system (CNS) epitopes are also found in sera of most PANDAS subjects (Yaddanapudi, K. et al. (2010) *Mol. Psychiatry* 15:712-726). Thus, several neuropsychiatric disorders have been associated with immune and autoimmune components, making them suitable for therapies that include PI3K-δ and/or PI3K-γ inhibition.

In certain embodiments, a method of treating (e.g., reducing or ameliorating one or more symptoms of) a neuropsychiatric disorder, (e.g., an autoimmune brain disorder), using a PI3K-δ and/or PI3K-γ inhibitor is described, alone or in combination therapy. For example, one or more PI3K-δ and/or PI3K-γ inhibitors described herein can be used alone or in combination with any suitable therapeutic agent and/or modalities, e.g., dietary supplement, for treatment of neuropsychiatric disorders. Exemplary neuropsychiatric disorders that can be treated with the PI3K-δ and/or PI3K-γ inhibitors described herein include, but are not limited to, PANDAS disorders, Sydenham's chorea, Tourette's syndrome, obsessive compulsive disorder, attention deficit/hyperactivity disorder, anorexia nervosa, depression, and autism spectrum disorders. Pervasive Developmental Disorder (PDD) is an exemplary class of autism spectrum disorders that includes Autistic Disorder, Asperger's Disorder, Childhood Disintegrative Disorder (CDD), Rett's Disorder and PDD-Not Otherwise Specified (PDD-NOS). Animal models for evaluating the activity of the PI3K-δ and/or PI3K-γ inhibitor are known in the art. For example, a mouse model of PANDAS disorders is described in, e.g., Yaddanapudi, K. et al. (2010) supra; and Hoffman, K. I. et al. (2004) *J. Neurosci.* 24:1780-1791.

In some embodiments, provided herein is a method for treating rheumatoid arthritis or asthma in a subject, or for reducing a rheumatoid arthritis-associated symptom or an asthma-associated symptom in a subject, comprising administering an effective amount of a PI3K-γ inhibitor to a subject in need thereof, wherein one or more of the adverse effects associated with administration of inhibitors for one or more other isoforms of PI3K are reduced. In one embodiment, the one or more other isoforms of PI3K is PI3K-α, PI3K-β, and/or PI3K-δ. In one embodiment, the one or more other isoforms of PI3K is PI3K-α and/or PI3K-β. In one embodiment, the method is for treating rheumatoid arthritis in a subject, or for reducing a rheumatoid arthritis-associated symptom in a subject. In another embodiment, the method is for treating asthma in a subject, or for reducing an asthma-associated symptom in a subject.

In some embodiments, provided herein are methods of using a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, to treat disease conditions, including, but not limited to, diseases associated with malfunctioning of one or more types of PI3 kinase. In one embodiment, a detailed description of conditions and disorders mediated by p110δ

kinase activity is set forth in Sadu et al., WO 01/81346, which is incorporated herein by reference in its entirety for all purposes.

In some embodiments, the disclosure relates to a method of treating a hyperproliferative disorder in a subject that comprises administering to said subject a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein. In some embodiments, said method relates to the treatment of cancer such as acute myeloid leukemia, thymus, brain, lung, squamous cell, skin, eye, retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal, bladder, gastric, stomach, pancreatic, bladder, breast, cervical, head, neck, renal, kidney, liver, ovarian, prostate, colorectal, esophageal, testicular, gynecological, thyroid, CNS, PNS, AIDS-related (e.g., Lymphoma and Kaposi's Sarcoma) or viral-induced cancer. In some embodiments, said method relates to the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e.g., psoriasis), restenosis, or prostate (e.g., benign prostatic hypertrophy (BPH)).

Patients that can be treated with a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, according to the methods as provided herein include, for example, but not limited to, patients that have been diagnosed as having psoriasis; restenosis; atherosclerosis; BPH; breast cancer such as a ductal carcinoma, lobular carcinoma, medullary carcinomas, colloid carcinomas, tubular carcinomas, and inflammatory breast cancer; ovarian cancer, including epithelial ovarian tumors such as adenocarcinoma in the ovary and an adenocarcinoma that has migrated from the ovary into the abdominal cavity; uterine cancer; cervical cancer such as adenocarcinoma in the cervix epithelial including squamous cell carcinoma and adenocarcinomas; prostate cancer, such as a prostate cancer selected from the following: an adenocarcinoma or an adenocarcinoma that has migrated to the bone; pancreatic cancer such as epitheliod carcinoma in the pancreatic duct tissue and an adenocarcinoma in a pancreatic duct; bladder cancer such as a transitional cell carcinoma in urinary bladder, urothelial carcinomas (transitional cell carcinomas), tumors in the urothelial cells that line the bladder, squamous cell carcinomas, adenocarcinomas, and small cell cancers; leukemia such as acute myeloid leukemia (AML), acute lymphocytic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, hairy cell leukemia, myelodysplasia, myeloproliferative disorders, NK cell leukemia (e.g., blastic plasmacytoid dendritic cell neoplasm), acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), mastocytosis, chronic lymphocytic leukemia (CLL), multiple myeloma (MM), and myelodysplastic syndrome (MDS); bone cancer; lung cancer such as non-small cell lung cancer (NSCLC), which is divided into squamous cell carcinomas, adenocarcinomas, and large cell undifferentiated carcinomas, and small cell lung cancer; skin cancer such as basal cell carcinoma, melanoma, squamous cell carcinoma and actinic keratosis, which is a skin condition that sometimes develops into squamous cell carcinoma; eye retinoblastoma; cutaneous or intraocular (eye) melanoma; primary liver cancer; kidney cancer; thyroid cancer such as papillary, follicular, medullary and anaplastic; lymphoma such as diffuse large B-cell lymphoma, B-cell immunoblastic lymphoma, NK cell lymphoma (e.g., blastic plasmacytoid dendritic cell neoplasm), and Burkitt lymphoma; Kaposi's Sarcoma; viral-induced cancers including hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatocellular carcinoma; human lymphotropic virus-type 1 (HTLV-1) and adult T-cell leukemia/lymphoma; and human papilloma virus (HPV) and cervical cancer; central nervous system cancers (CNS) such as primary brain tumor, which includes gliomas (astrocytoma, anaplastic astrocytoma, or glioblastoma multiforme), oligodendroglioma, ependymoma, meningioma, lymphoma, schwannoma, and medulloblastoma; peripheral nervous system (PNS) cancers such as acoustic neuromas and malignant peripheral nerve sheath tumor (MPNST) including neurofibromas and schwannomas, malignant fibrocytoma, malignant fibrous histiocytoma, malignant meningioma, malignant mesothelioma, and malignant mixed Müllerian tumor; oral cavity and oropharyngeal cancers such as, hypopharyngeal cancer, laryngeal cancer, nasopharyngeal cancer, and oropharyngeal cancer; stomach cancers such as lymphomas, gastric stromal tumors, and carcinoid tumors; testicular cancers such as germ cell tumors (GCTs), which include seminomas and nonseminomas, and gonadal stromal tumors, which include Leydig cell tumors and Sertoli cell tumors; thymus cancer such as to thymomas, thymic carcinomas, Hodgkin lymphoma, non-Hodgkin lymphomas carcinoids or carcinoid tumors; rectal cancer; and colon cancer.

Patients that can be treated with compounds provided herein, or pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative of said compounds, according to the methods provided herein include, for example, patients that have been diagnosed as having conditions including, but not limited to, acoustic neuroma, adenocarcinoma, adrenal gland cancer, anal cancer, angiosarcoma (e.g., lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma), benign monoclonal gammopathy, biliary cancer (e.g., cholangiocarcinoma), bladder cancer, breast cancer (e.g., adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast), brain cancer (e.g., meningioma; glioma, e.g., astrocytoma, oligodendroglioma; medulloblastoma), bronchus cancer, cervical cancer (e.g., cervical adenocarcinoma), choriocarcinoma, chordoma, craniopharyngioma, colorectal cancer (e.g., colon cancer, rectal cancer, colorectal adenocarcinoma), epithelial carcinoma, ependymoma, endotheliosarcoma (e.g., Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma), endometrial cancer, esophageal cancer (e.g., adenocarcinoma of the esophagus, Barrett's adenocarinoma), Ewing sarcoma, familiar hypereosinophilia, gastric cancer (e.g., stomach adenocarcinoma), gastrointestinal stromal tumor (GIST), head and neck cancer (e.g., head and neck squamous cell carcinoma, oral cancer (e.g., oral squamous cell carcinoma (OSCC)), heavy chain disease (e.g., alpha chain disease, gamma chain disease, mu chain disease), hemangioblastoma, inflammatory myofibroblastic tumors, immunocytic amyloidosis, kidney cancer (e.g., nephroblastoma a.k.a. Wilms' tumor, renal cell carcinoma), liver cancer (e.g., hepatocellular cancer (HCC), malignant hepatoma), lung cancer (e.g., bronchogenic carcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung), leukemia (e.g., acute lymphocytic leukemia (ALL), which includes B-lineage ALL and T-lineage ALL, chronic lymphocytic leukemia (CLL), prolymphocytic leukemia (PLL), hairy cell leukemia (HLL) and Waldenstrom's macroglobulinemia (WM); peripheral T cell lymphomas (PTCL), adult T cell leukemia/lymphoma (ATL), cutaneous T-cell lymphoma (CTCL), large granular lymphocytic leukemia (LGF), Hodgkin's disease and Reed-Stemberg disease; acute myelocytic leukemia (AML), chronic myelocytic leukemia

(CML), chronic lymphocytic leukemia (CLL)), lymphoma (e.g., Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL)), leiomyosarcoma (LMS), mastocytosis (e.g., systemic mastocytosis), multiple myeloma (MM), myelodysplastic syndrome (MDS), mesothelioma, myeloproliferative disorder (MPD) (e.g., polycythemia Vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) a.k.a. myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)), neuroblastoma, neurofibroma (e.g., neurofibromatosis (NF) type 1 or type 2, schwannomatosis), neuroendocrine cancer (e.g., gastroenteropancreatic neuroendoctrine tumor (GEP-NET), carcinoid tumor), osteosarcoma, ovarian cancer (e.g., cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma), Paget's disease of the vulva, Paget's disease of the penis, papillary adenocarcinoma, pancreatic cancer (e.g., pancreatic andenocarcinoma, intraductal papillary mucinous neoplasm (IPMN)), pinealoma, primitive neuroectodermal tumor (PNT), prostate cancer (e.g., prostate adenocarcinoma), rhabdomyosarcoma, retinoblastoma, salivary gland cancer, skin cancer (e.g., squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)), small bowel cancer (e.g., appendix cancer), soft tissue sarcoma (e.g., malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma), sebaceous gland carcinoma, sweat gland carcinoma, synovioma, testicular cancer (e.g., seminoma, testicular embryonal carcinoma), thyroid cancer (e.g., papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary thyroid cancer), and Waldenstrom's macroglobulinemia.

Without being limited by a particular theory, in one embodiment, the cancer or disease being treated or prevented, such as a blood disorder or hematologic malignancy, has a high expression level of one or more PI3K isoform(s) (e.g., PI3K-α, PI3K-β, PI3K-δ, or PI3K-γ, or a combination thereof). In one embodiment, the cancer or disease that can be treated or prevented by methods, compositions, or kits provided herein includes a blood disorder or a hematologic malignancy, including, but not limited to, myeloid disorder, lymphoid disorder, leukemia, lymphoma, myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), mast cell disorder, and myeloma (e.g., multiple myeloma), among others. In one embodiment, the blood disorder or the hematologic malignancy includes, but is not limited to, acute lymphoblastic leukemia (ALL), T-cell ALL (T-ALL), B-cell ALL (B-ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), blast phase CML, small lymphocytic lymphoma (SLL), CLL/SLL, blast phase CLL, Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), B-cell NHL, T-cell NHL, indolent NHL (iNHL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), aggressive B-cell NHL, B-cell lymphoma (BCL), Richter's syndrome (RS), T-cell lymphoma (TCL), peripheral T-cell lymphoma (PTCL), cutaneous T-cell lymphoma (CTCL), transformed mycosis fungoides, Sézary syndrome, anaplastic large-cell lymphoma (ALCL), follicular lymphoma (FL), Waldenström macroglobulinemia (WM), lymphoplasmacytic lymphoma, Burkitt lymphoma, multiple myeloma (MM), amyloidosis, MPD, essential thrombocytosis (ET), myelofibrosis (MF), polycythemia vera (PV), chronic myelomonocytic leukemia (CMML), myelodysplastic syndrome (MDS), angioimmunoblastic lymphoma, high-risk MDS, and low-risk MDS. In one embodiment, the hematologic malignancy is relapsed. In one embodiment, the hematologic malignancy is refractory. In one embodiment, the cancer or disease is in a pediatric patient (including an infantile patient). In one embodiment, the cancer or disease is in an adult patient. Additional embodiments of a cancer or disease being treated or prevented by methods, compositions, or kits provided herein are described herein elsewhere.

In exemplary embodiments, the cancer or hematologic malignancy is CLL. In exemplary embodiments, the cancer or hematologic malignancy is CLL/SLL. In exemplary embodiments, the cancer or hematologic malignancy is blast phase CLL. In exemplary embodiments, the cancer or hematologic malignancy is SLL.

In exemplary embodiments, the cancer or hematologic malignancy is iNHL. In exemplary embodiments, the cancer or hematologic malignancy is DLBCL. In exemplary embodiments, the cancer or hematologic malignancy is B-cell NHL (e.g., aggressive B-cell NHL). In exemplary embodiments, the cancer or hematologic malignancy is MCL. In exemplary embodiments, the cancer or hematologic malignancy is RS. In exemplary embodiments, the cancer or hematologic malignancy is AML. In exemplary embodiments, the cancer or hematologic malignancy is MM. In exemplary embodiments, the cancer or hematologic malignancy is ALL. In exemplary embodiments, the cancer or hematologic malignancy is T-ALL. In exemplary embodiments, the cancer or hematologic malignancy is B-ALL. In exemplary embodiments, the cancer or hematologic malignancy is TCL. In exemplary embodiments, the cancer or hematologic malignancy is ALCL. In exemplary embodiments, the cancer or hematologic malignancy is leukemia. In exemplary embodiments, the cancer or hematologic malignancy is lymphoma. In exemplary embodiments, the cancer or hematologic malignancy is T-cell lymphoma. In exemplary embodiments, the cancer or hematologic malignancy is MDS (e.g., low grade MDS). In exemplary embodiments, the cancer or hematologic malignancy is MPD. In exemplary embodiments, the cancer or hematologic malignancy is a mast cell disorder. In exemplary embodiments, the cancer or hematologic malignancy is Hodgkin lymphoma (HL). In exemplary embodiments, the cancer or hematologic malignancy is non-Hodgkin lymphoma. In exemplary embodiments, the cancer or hematologic malignancy is PTCL. In exemplary embodiments, the cancer or hematologic malignancy is CTCL (e.g., mycosis fungoides or Sézary syndrome). In exemplary embodiments, the cancer or hematologic malignancy is WM. In exemplary embodiments, the cancer or hematologic malignancy is CML. In exemplary embodiments, the cancer or hematologic malignancy is FL. In exemplary embodiments, the cancer or hematologic malignancy is transformed mycosis fungoides. In exemplary embodiments, the cancer or hematologic malignancy is Sézary syndrome. In exemplary embodiments, the cancer or hematologic malignancy is acute T-cell leukemia. In exemplary embodiments, the cancer or hematologic malignancy is acute B-cell leukemia. In exemplary embodiments, the cancer or hematologic malignancy is Burkitt lymphoma. In exemplary embodiments, the cancer or hematologic malignancy is myeloproliferative neoplasms. In exemplary embodiments, the cancer or hematologic malignancy is splenic marginal zone. In exemplary embodiments, the cancer or hematologic malignancy is nodal marginal zone. In exemplary embodiments, the cancer or hematologic malignancy is extranodal marginal zone.

In one embodiment, the cancer or hematologic malignancy is a B cell lymphoma. In a specific embodiment, provided

herein is a method of treating or managing a B cell lymphoma comprising administering to a patient a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof. Also provided herein is a method of treating or lessening one or more of the symptoms associated with a B cell lymphoma comprising administering to a patient a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof. In one embodiment, the B cell lymphoma is iNHL. In another embodiment, the B cell lymphoma is follicular lymphoma. In another embodiment, the B cell lymphoma is Waldenstrom macroglobulinemia (lymphoplasmacytic lymphoma). In another embodiment, the B cell lymphoma is marginal zone lymphoma (MZL). In another embodiment, the B cell lymphoma is MCL. In another embodiment, the B cell lymphoma is HL. In another embodiment, the B cell lymphoma is aNHL. In another embodiment, the B cell lymphoma is DLBCL. In another embodiment, the B cell lymphoma is Richters lymphoma.

In one embodiment, the cancer or hematologic malignancy is a T cell lymphoma. In a specific embodiment, provided herein is a method of treating or managing a T cell lymphoma comprising administering to a patient a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof. Also provided herein is a method of treating or lessening one or more of the symptoms associated with a T cell lymphoma comprising administering to a patient a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof. In one embodiment, the T cell lymphoma is peripheral T cell lymphoma (PTCL). In another embodiment, the T cell lymphoma is cutaneous T cell lymphoma (CTCL).

In one embodiment, the cancer or hematologic malignancy is Sézary syndrome. In a specific embodiment, provided herein is a method of treating or managing Sézary syndrome comprising administering to a patient a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof. Also provided herein is a method of treating or lessening one or more of the symptoms associated with Sézary syndrome comprising administering to a patient a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof. The symptoms associated with Sézary syndrome include, but are not limited to, epidermotropism by neoplastic CD4+ lymphocytes, Pautrier's microabscesses, erythroderma, lymphadenopathy, atypical T cells in the peripheral blood, and hepatosplenomegaly In one embodiment, the therapeutically effective amount for treating or managing Sézary syndrome is from about 25 mg to 75 mg, administered twice daily. In other embodiments, the therapeutically effective amount is from about 50 mg to about 75 mg, from about 30 mg to about 65 mg, from about 45 mg to about 60 mg, from about 30 mg to about 50 mg, or from about 55 mg to about 65 mg, each of which is administered twice daily. In one embodiment, the effective amount is about 60 mg, administered twice daily.

In one embodiment, the cancer or hematologic malignancy is relapsed. In one embodiment, the cancer or hematologic malignancy is refractory. In certain embodiments, the cancer being treated or prevented is a specific sub-type of cancer described herein. In certain embodiments, the hematologic malignancy being treated or prevented is a specific sub-type of hematologic malignancy described herein. Certain classifications of type or sub-type of a cancer or hematologic malignancy provided herein is known in the art. Without being limited by a particular theory, it is believed that many of the cancers that become relapsed or refractory develop resistance to the particular prior therapy administered to treat the cancers. Thus, without being limited by a particular theory, a compound provided herein can provide a second line therapy by providing an alternative mechanism to treat cancers different from those mechanisms utilized by certain prior therapies. Accordingly, in one embodiment, provided herein is a method of treating or managing cancer or hematologic malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, wherein the cancer or hematologic malignancy is relapsed after, or refractory to, a prior therapy.

In exemplary embodiments, the cancer or hematologic malignancy is refractory iNHL. In exemplary embodiments, the cancer or hematologic malignancy is refractory CLL. In exemplary embodiments, the cancer or hematologic malignancy is refractory SLL. In exemplary embodiments, the cancer or hematologic malignancy is refractory to rituximab therapy. In exemplary embodiments, the cancer or hematologic malignancy is refractory to chemotherapy. In exemplary embodiments, the cancer or hematologic malignancy is refractory to radioimmunotherapy (RIT). In exemplary embodiments, the cancer or hematologic malignancy is iNHL, FL, splenic marginal zone, nodal marginal zone, extranodal marginal zone, or SLL, the cancer or hematologic malignancy is refractory to rituximab therapy, chemotherapy, and/or RIT.

In another exemplary embodiment, the cancer or hematologic malignancy is lymphoma, and the cancer is relapsed after, or refractory to, the treatment by a BTK inhibitor such as, but not limited to, ibrutinib. In another exemplary embodiment, the cancer or hematologic malignancy is CLL, and the cancer is relapsed after, or refractory to, the treatment by a BTK inhibitor such as, but not limited to, ibrutinib and AVL-292.

In one embodiment, provided herein is a method of treating an inflammation disorder, including autoimmune diseases in a subject. The method comprises administering to said subject a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein. Examples of autoimmune diseases include but are not limited to acute disseminated encephalomyelitis (ADEM), Addison's disease, antiphospholipid antibody syndrome (APS), aplastic anemia, autoimmune hepatitis, autoimmune skin disease, coeliac disease, Crohn's disease, Diabetes mellitus (type 1), Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome (GBS), Hashimoto's disease, lupus erythematosus, multiple sclerosis, myasthenia gravis, opsoclonus myoclonus syndrome (OMS), optic neuritis, Ord's thyroiditis, oemphigus, polyarthritis, primary biliary cirrhosis, psoriasis, rheumatoid arthritis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis (also known as "giant cell arteritis"), warm autoimmune hemolytic anemia, Wegener's granulomatosis, alopecia universalis (e.g., inflammatory alopecia), Chagas disease, chronic fatigue syndrome, dysautonomia, endometriosis, hidradenitis suppurativa, interstitial cystitis, neuromyotonia, sarcoidosis, scleroderma, ulcerative colitis, vitiligo, and vulvodynia. Other disorders include bone-resorption disorders and thrombosis.

Inflammation takes on many forms and includes, but is not limited to, acute, adhesive, atrophic, catarrhal, chronic, cirrhotic, diffuse, disseminated, exudative, fibrinous, fibrosing,

focal, granulomatous, hyperplastic, hypertrophic, interstitial, metastatic, necrotic, obliterative, parenchymatous, plastic, productive, proliferous, pseudomembranous, purulent, sclerosing, seroplastic, serous, simple, specific, subacute, suppurative, toxic, traumatic, and/or ulcerative inflammation.

Exemplary inflammatory conditions include, but are not limited to, inflammation associated with acne, anemia (e.g., aplastic anemia, haemolytic autoimmune anaemia), asthma, arteritis (e.g., polyarteritis, temporal arteritis, periarteritis nodosa, Takayasu's arteritis), arthritis (e.g., crystalline arthritis, osteoarthritis, psoriatic arthritis, gout flare, gouty arthritis, reactive arthritis, rheumatoid arthritis and Reiter's arthritis), ankylosing spondylitis, amylosis, amyotrophic lateral sclerosis, autoimmune diseases, allergies or allergic reactions, atherosclerosis, bronchitis, bursitis, chronic prostatitis, conjunctivitis, Chagas disease, chronic obstructive pulmonary disease, cermatomyositis, diverticulitis, diabetes (e.g., type I diabetes mellitus, type 2 diabetes mellitus), a skin condition (e.g., psoriasis, eczema, burns, dermatitis, pruritus (itch)), endometriosis, Guillain-Barre syndrome, infection, ischaemic heart disease, Kawasaki disease, glomerulonephritis, gingivitis, hypersensitivity, headaches (e.g., migraine headaches, tension headaches), ileus (e.g., postoperative ileus and ileus during sepsis), idiopathic thrombocytopenic purpura, interstitial cystitis (painful bladder syndrome), gastrointestinal disorder (e.g., selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (e.g., eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym GERD), inflammatory bowel disease (IBD) (e.g., Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)), lupus, multiple sclerosis, morphea, myeasthenia gravis, myocardial ischemia, nephrotic syndrome, pemphigus vulgaris, pernicious aneaemia, peptic ulcers, polymyositis, primary biliary cirrhosis, neuroinflammation associated with brain disorders (e.g., Parkinson's disease, Huntington's disease, and Alzheimer's disease), prostatitis, chronic inflammation associated with cranial radiation injury, pelvic inflammatory disease, polymyalgia rheumatic, reperfusion injury, regional enteritis, rheumatic fever, systemic lupus erythematosus, scleroderma, scierodoma, sarcoidosis, spondyloarthopathies, Sjogren's syndrome, thyroiditis, transplantation rejection, tendonitis, trauma or injury (e.g., frostbite, chemical irritants, toxins, scarring, burns, physical injury), vasculitis, vitiligo and Wegener's granulomatosis. In certain embodiments, the inflammatory disorder is selected from arthritis (e.g., rheumatoid arthritis), inflammatory bowel disease, inflammatory bowel syndrome, asthma, psoriasis, endometriosis, interstitial cystitis and prostatistis. In certain embodiments, the inflammatory condition is an acute inflammatory condition (e.g., for example, inflammation resulting from infection). In certain embodiments, the inflammatory condition is a chronic inflammatory condition (e.g., conditions resulting from asthma, arthritis and inflammatory bowel disease). The compounds can also be useful in treating inflammation associated with trauma and non-inflammatory myalgia.

Immune disorders, such as auto-immune disorders, include, but are not limited to, arthritis (including rheumatoid arthritis, spondyloarthopathies, gouty arthritis, degenerative joint diseases such as osteoarthritis, systemic lupus erythematosus, Sjogren's syndrome, ankylosing spondylitis, undifferentiated spondylitis, Behcet's disease, haemolytic autoimmune anaemias, multiple sclerosis, amyotrophic lateral sclerosis, amylosis, acute painful shoulder, psoriatic, and juvenile arthritis), asthma, atherosclerosis, osteoporosis, bronchitis, tendonitis, bursitis, skin condition (e.g., psoriasis, eczema, burns, dermatitis, pruritus (itch)), enuresis, eosinophilic disease, gastrointestinal disorder (e.g., selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (e.g., eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym GERD), inflammatory bowel disease (IBD) (e.g., Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)), relapsing polychondritis (e.g., atrophic polychondritis and systemic polychondromalacia), and disorders ameliorated by a gastroprokinetic agent (e.g., ileus, postoperative ileus and ileus during sepsis; gastroesophageal reflux disease (GORD, or its synonym GERD); eosinophilic esophagitis, gastroparesis such as diabetic gastroparesis; food intolerances and food allergies and other functional bowel disorders, such as non-ulcerative dyspepsia (NUD) and non-cardiac chest pain (NCCP, including costo-chondritis)). In certain embodiments, a method of treating inflammatory or autoimmune diseases is provided comprising administering to a subject (e.g., a mammal) a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, that selectively inhibit PI3K-δ and/or PI3K-γ as compared to all other type I PI3 kinases. Such selective inhibition of PI3K-δ and/or PI3K-γ can be advantageous for treating any of the diseases or conditions described herein. For example, selective inhibition of PI3K-δ and/or PI3K-γ can inhibit inflammatory responses associated with inflammatory diseases, autoimmune disease, or diseases related to an undesirable immune response including, but not limited to asthma, emphysema, allergy, dermatitis, rheumatoid arthritis, psoriasis, lupus erythematosus, anaphylaxsis, or graft versus host disease. Selective inhibition of PI3K-δ and/or PI3K-γ can further provide for a reduction in the inflammatory or undesirable immune response without a concomitant reduction in the ability to reduce a bacterial, viral, and/or fungal infection. Selective inhibition of both PI3K-δ and PI3K-γ can be advantageous for inhibiting the inflammatory response in the subject to a greater degree than that would be provided for by inhibitors that selectively inhibit PI3K-δ or PI3K-γ alone. In one aspect, one or more of the subject methods are effective in reducing antigen specific antibody production in vivo by about 2-fold, 3-fold, 4-fold, 5-fold, 7.5-fold, 10-fold, 25-fold, 50-fold, 100-fold, 250-fold, 500-fold, 750-fold, or about 1000-fold or more. In another aspect, one or more of the subject methods are effective in reducing antigen specific IgG3 and/or IgGM production in vivo by about 2-fold, 3-fold, 4-fold, 5-fold, 7.5-fold, 10-fold, 25-fold, 50-fold, 100-fold, 250-fold, 500-fold, 750-fold, or about 1000-fold or more.

In one aspect, one of more of the subject methods are effective in ameliorating symptoms associated with rheumatoid arthritis including, but not limited to a reduction in the swelling of joints, a reduction in serum anti-collagen levels, and/or a reduction in joint pathology such as bone resorption, cartilage damage, pannus, and/or inflammation. In another aspect, the subject methods are effective in reducing ankle inflammation by at least about 2%, 5%, 10%, 15%, 20%, 25%, 30%, 50%, or 60%, or about 75% to 90%. In another aspect, the subject methods are effective in reducing knee

inflammation by at least about 2%, 5%, 10%, 15%, 20%, 25%, 30%, 50%, or 60%, or about 75% to 90% or more. In still another aspect, the subject methods are effective in reducing serum anti-type II collagen levels by at least about 10%, 12%, 15%, 20%, 24%, 25%, 30%, 35%, 50%, 60%, 75%, 80%, 86%, or 87%, or about 90% or more. In another aspect, the subject methods are effective in reducing ankle histopathology scores by about 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 75%, 80%, or 90%, or more. In still another aspect, the subject methods are effective in reducing knee histopathology scores by about 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 75%, 80%, or 90%, or more.

In some embodiments, provided herein are methods for treating disorders or conditions in which the δ isoform of PI3K is implicated to a greater extent than other PI3K isoforms such as PI3K-α and/or PI3K-β. In some embodiments, provided herein are methods for treating disorders or conditions in which the γ isoform of PI3K is implicated to a greater extent than other PI3K isoforms such as PI3K-α and/or PI3K-β. Selective inhibition of PI3K-δ and/or PI3K-γ can provide advantages over using less selective compounds which inhibit PI3K-α and/or PI3K-β, such as an improved side effects profile or lessened reduction in the ability to reduce a bacterial, viral, and/or fungal infection.

In other embodiments, provided herein are methods of using a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, to treat respiratory diseases including, but not limited to, diseases affecting the lobes of lung, pleural cavity, bronchial tubes, trachea, upper respiratory tract, or the nerves and muscle for breathing. For example, methods are provided to treat obstructive pulmonary disease. Chronic obstructive pulmonary disease (COPD) is an umbrella term for a group of respiratory tract diseases that are characterized by airflow obstruction or limitation. Conditions included in this umbrella term include, but are not limited to: chronic bronchitis, emphysema, and bronchiectasis.

In another embodiment, a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein is used for the treatment of asthma. Also, a compound provided herein, or a pharmaceutically acceptable form thereof, or a pharmaceutical composition described herein, can be used for the treatment of endotoxemia and sepsis. In one embodiment, the compounds or pharmaceutical compositions described herein are used to for the treatment of rheumatoid arthritis (RA). In yet another embodiment, the compounds or pharmaceutical compositions described herein is used for the treatment of contact or atopic dermatitis. Contact dermatitis includes irritant dermatitis, phototoxic dermatitis, allergic dermatitis, photoallergic dermatitis, contact urticaria, systemic contact-type dermatitis and the like. Irritant dermatitis can occur when too much of a substance is used on the skin of when the skin is sensitive to certain substance. Atopic dermatitis, sometimes called eczema, is a kind of dermatitis, an atopic skin disease.

In some embodiments, the disclosure provides a method of treating diseases related to vasculogenesis or angiogenesis in a subject that comprises administering to said subject a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein. In some embodiments, said method is for treating a disease selected from tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis and chronic inflammatory demyelinating polyneuropathy, atherosclerosis, inflammatory bowel disease, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

In addition, the compounds described herein can be used for the treatment of arteriosclerosis, including atherosclerosis. Arteriosclerosis is a general term describing any hardening of medium or large arteries. Atherosclerosis is a hardening of an artery specifically due to an atheromatous plaque.

In some embodiments, provided herein is a method of treating a cardiovascular disease in a subject that comprises administering to said subject a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein. Examples of cardiovascular conditions include, but are not limited to, atherosclerosis, restenosis, vascular occlusion and carotid obstructive disease.

In some embodiments, the disclosure relates to a method of treating diabetes in a subject that comprises administering to said subject a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein.

In addition, a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, can be used to treat acne. In certain embodiments, the inflammatory condition and/or immune disorder is a skin condition. In some embodiments, the skin condition is pruritus (itch), psoriasis, eczema, burns or dermatitis. In certain embodiments, the skin condition is psoriasis. In certain embodiments, the skin condition is pruritis.

In certain embodiments, the inflammatory disorder and/or the immune disorder is a gastrointestinal disorder. In some embodiments, the gastrointestinal disorder is selected from gastrointestinal disorder (e.g., selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (e.g., eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym GERD), inflammatory bowel disease (IBD) (e.g., Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)). In certain embodiments, the gastrointestinal disorder is inflammatory bowel disease (IBD).

Further, a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, can be used for the treatment of glomerulonephritis. Glomerulonephritis is a primary or secondary autoimmune renal disease characterized by inflammation of the glomeruli. It can be asymptomatic, or present with hematuria and/or proteinuria. There are many recognized types, divided in acute, subacute or chronic glomerulonephritis.

Causes are infectious (bacterial, viral or parasitic pathogens), autoimmune or paraneoplastic.

In some embodiments, provided herein are compounds, or pharmaceutically acceptable forms (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, for the treatment of multiorgan failure. Also provided herein are compounds, or pharmaceutically acceptable forms (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, for the treatment of liver diseases (including diabetes), gall bladder disease (including gallstones), pancreatitis or kidney disease (including proliferative glomerulonephritis and diabetes-induced renal disease) or pain in a subject.

In some embodiments, provided herein are compounds, or pharmaceutically acceptable forms (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, for the prevention of blastocyte implantation in a subject.

In some embodiments, provided herein are compounds, or pharmaceutically acceptable forms (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, for the treatment of disorders involving platelet aggregation or platelet adhesion, including, but not limited to, Idiopathic thrombocytopenic purpura, Bernard-Soulier syndrome, Glanzmann's thrombasthenia, Scott's syndrome, von Willebrand disease, Hermansky-Pudlak Syndrome, and Gray platelet syndrome.

In some embodiments, provided herein are compounds, or pharmaceutically acceptable forms (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, for the treatment of a disease which is skeletal muscle atrophy, skeletal or muscle hypertrophy. In some embodiments, provided herein are compounds, or pharmaceutically acceptable forms (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, for the treatment of disorders that include, but are not limited to, cancers as discussed herein, transplantation-related disorders (e.g., lowering rejection rates, graft-versus-host disease, etc.), muscular sclerosis (MS), allergic disorders (e.g., arthritis, allergic encephalomyelitis) and other immunosuppressive-related disorders, metabolic disorders (e.g., diabetes), reducing intimal thickening following vascular injury, and misfolded protein disorders (e.g., Alzheimer's Disease, Gaucher's Disease, Parkinson's Disease, Huntington's Disease, cystic fibrosis, macular degeneration, retinitis pigmentosa, and prion disorders) (as mTOR inhibition can alleviate the effects of misfolded protein aggregates). The disorders also include hamartoma syndromes, such as tuberous sclerosis and Cowden Disease (also termed Cowden syndrome and multiple hamartoma syndrome).

Additionally, a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, can be used for the treatment of bursitis, lupus, acute disseminated encephalomyelitis (ADEM), Addison's disease, antiphospholipid antibody syndrome (APS), amyloidosis (including systemic and localized amyloidosis; and primary and secondary amyloidosis), aplastic anemia, autoimmune hepatitis, coeliac disease, crohn's disease, diabetes mellitus (type 1), eosinophilic gastroenterides, goodpasture's syndrome, graves' disease, guillain-barre syndrome (GBS), hashimoto's disease, inflammatory bowel disease, lupus erythematosus (including cutaneous lupus erythematosus and systemic lupus erythematosus), myasthenia gravis, opsoclonus myoclonus syndrome (OMS), optic neuritis, ord's thyroiditis, ostheoarthritis, uveoretinitis, pemphigus, polyarthritis, primary biliary cirrhosis, reiter's syndrome, takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, wegener's granulomatosis, alopecia universalis, chagas' disease, chronic fatigue syndrome, dysautonomia, endometriosis, hidradenitis suppurativa, interstitial cystitis, neuromyotonia, sarcoidosis, scleroderma, ulcerative colitis, vitiligo, vulvodynia, appendicitis, arteritis, arthritis, blepharitis, bronchiolitis, bronchitis, cervicitis, cholangitis, cholecystitis, chorioamnionitis, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatomyositis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, gingivitis, hepatitis, hidradenitis, ileitis, iritis, laryngitis, mastitis, meningitis, myelitis, myocarditis, myositis, nephritis, omphalitis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, uveitis (e.g., ocular uveitis), vaginitis, vasculitis, or vulvitis.

Further, the compounds provided herein may be used for the treatment of Perennial allergic rhinitis, Mesenteritis, Peritonitis, Acrodermatitis, Angiodermatitis, Atopic dermatitis, Contact dermatitis, Eczema, Erythema multiforme, Intertrigo, Stevens Johnson syndrome, Toxic epidermal necrolysis, Skin allergy, Severe allergic reaction/anaphylaxis, Allergic granulomatosis, Wegener granulomatosis, Allergic conjunctivitis, Chorioretinitis, Conjunctivitis, Infectious keratoconjunctivitis, Keratoconjunctivitis, Ophthalmia neonatorum, Trachoma, Uveitis, Ocular inflammation, Blepharoconjunctivitis, Mastitis, Gingivitis, Pericoronitis, Pharyngitis, Rhinopharyngitis, Sialadenitis, Musculoskeletal system inflammation, Adult onset Stills disease, Behcets disease, Bursitis, Chondrocalcinosis, Dactylitis, Felty syndrome, Gout, Infectious arthritis, Lyme disease, Inflammatory osteoarthritis, Periarthritis, Reiter syndrome, Ross River virus infection, Acute Respiratory, Distress Syndrome, Acute bronchitis, Acute sinusitis, Allergic rhinitis, Asthma, Severe refractory asthma, Pharyngitis, Pleurisy, Rhinopharyngitis, Seasonal allergic rhinitis, Sinusitis, Status asthmaticus, Tracheobronchitis, Rhinitis, Serositis, Meningitis, Neuromyelitis optica, Poliovirus infection, Alport syndrome, Balanitis, Epididymitis, Epididymo orchitis, Focal segmental, Glomerulosclerosis, Glomerulonephritis, IgA Nephropathy (Berger's Disease), Orchitis, Parametritis, Pelvic inflammatory disease, Prostatitis, Pyelitis, Pyelocystitis, Pyelonephritis, Wegener granulomatosis, Hyperuricemia, Aortitis, Arteritis, Chylopericarditis, Dressler syndrome, Endarteritis, Endocarditis, Extracranial temporal arteritis, HIV associated arteritis, Intracranial temporal arteritis, Kawasaki disease, Lymphangiophlebitis, Mondor disease, Periarteritis, or Pericarditis.

In other aspects, the compounds provided herein are used for the treatment of Autoimmune hepatitis, Jejunitis, Mesenteritis, Mucositis, Non alcoholic steatohepatitis, Non viral hepatitis, Autoimmune pancreatitis, Perihepatitis, Peritonitis, Pouchitis, Proctitis, Pseudomembranous colitis, Rectosigmoiditis, Salpingoperitonitis, Sigmoiditis, Steatohepatitis, Ulcerative colitis, Churg Strauss syndrome, Ulcerative proc-

titis, Irritable bowel syndrome, Gastrointestinal inflammation, Acute enterocolitis, Anusitis, Balser necrosis, Cholecystitis, Colitis, Crohns disease, Diverticulitis, Enteritis, Enterocolitis, Enterohepatitis, Eosinophilic esophagitis, Esophagitis, Gastritis, Hemorrhagic enteritis, Hepatitis, Hepatitis virus infection, Hepatocholangitis, Hypertrophic gastritis, Ileitis, Ileocecitis, Sarcoidosis, Inflammatory bowel disease, Ankylosing spondylitis, Rheumatoid arthritis, Juvenile rheumatoid arthritis, Psoriasis, Psoriatic arthritis, Lupus (cutaneous/systemic/nephritis), AIDS, Agammaglobulinemia, AIDS related complex, Brutons disease, Chediak Higashi syndrome, Common variable immunodeficiency, DiGeorge syndrome, Dysgammaglobulinemia, Immunoglobulindeficiency, Job syndrome, Nezelof syndrome, Phagocyte bactericidal disorder, Wiskott Aldrich syndrome, Asplenia, Elephantiasis, Hypersplenism, Kawasaki disease, Lymphadenopathy, Lymphedema, Lymphocele, Nonne Milroy Meige syndrome, Spleen disease, Splenomegaly, Thymoma, Thymus disease, Perivasculitis, Phlebitis, Pleuropericarditis, Polyarteritis nodosa, Vasculitis, Takayasus arteritis, Temporal arteritis, Thromboangiitis, Thromboangiitis obliterans, Thromboendocarditis, Thrombophlebitis, or COPD.

In another aspect, provided herein are methods of disrupting the function of a leukocyte or disrupting a function of an osteoclast. The method includes contacting the leukocyte or the osteoclast with a function disrupting amount of a compound provided herein.

In another aspect, provided herein are methods for the treatment of an ophthalmic disease by administering one or more of compounds provided herein, or pharmaceutically acceptable forms thereof, or pharmaceutical compositions as provided herein, to the eye of a subject.

Methods are further provided for administering the compounds provided herein via eye drop, intraocular injection, intravitreal injection, topically, or through the use of a drug eluting device, microcapsule, implant, or microfluidic device. In some cases, the compounds provided herein are administered with a carrier or excipient that increases the intraocular penetrance of the compound such as an oil and water emulsion with colloid particles having an oily core surrounded by an interfacial film.

In certain embodiments, provided herein are methods of treating, preventing, and/or managing a disease or a disorder using a compound, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, wherein the disease or disorder is: Crohn's disease; cutaneous lupus; multiple sclerosis; rheumatoid arthritis; and systemic lupus erythematosus.

In other embodiments, provided herein are methods of treating, preventing and/or managing a disease or a disorder using a compound, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, wherein the disease or disorder is: ankylosing spondylitis; chronic obstructive pulmonary disease; myasthenia gravis; ocular uveitis, psoriasis; and psoriatic arthritis.

In other embodiments, provided herein are methods of treating, preventing and/or managing a disease or a disorder using a compound, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, wherein the disease or disorder is: adult-onset Still's disease; inflammatory alopecia; amyloidosis; antiphospholipid syndrome; autoimmune hepatitis; autoimmune skin disease, Behcet's disease; chronic inflammatory demyelinating polyneuropathy; eosinophilic gastroenteritis; inflammatory myopathies, pemphigus, polymyalgia rheumatica; relapsing polychondritis; Sjorgen's syndrome; temporal arthritis; ulcerative colitis; vasculis; vitiligo, and Wegner's granulomatosis.

In other embodiments, provided herein are methods of treating, preventing and/or managing a disease or a disorder using a compound, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, wherein the disease or disorder is: gout flare; sacoidosis; and systemic sclerosis.

In certain embodiments, provided herein are methods of treating, preventing and/or managing a disease or a disorder using a compound, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, wherein the disease or disorder is: asthma; arthritis (e.g., rheumatoid arthritis and psoriatic arthritis); psoriasis; scleroderma; myositis (e.g., dermatomyositis); lupus (e.g., cutaneous lupus erythematosus ("CLE") or systemic lupus erythematosus ("SLE")); or Sjögren's syndrome.

Efficacy of a compound provided herein in treating, preventing and/or managing the disease or disorder can be tested using various animal models known in the art. For example: efficacy in treating, preventing and/or managing asthma can be assessed using ova induced asthma model described, for example, in Lee et al. (2006) *J Allergy Clin Immunol* 118(2): 403-9; efficacy in treating, preventing and/or managing arthritis (e.g., rheumatoid or psoriatic arthritis) can be assessed using autoimmune animal models described, for example, in Williams et al. (2010) *Chem Biol,* 17(2):123-34, WO 2009/088986, WO2009/088880, and WO 2011/008302; efficacy in treating, preventing and/or managing psoriasis can be assessed using transgenic or knockout mouse model with targeted mutations in epidermis, vasculature or immune cells, mouse model resulting from spontaneous mutations, and immuno-deficient mouse model with xenotransplantation of human skin or immune cells, all of which are described, for example, in Boehncke et al. (2007) *Clinics in Dermatology,* 25: 596-605; efficacy in treating, preventing and/or managing fibrosis or fibrotic condition can be assessed using the unilateral ureteral obstruction model of renal fibrosis (see Chevalier et al., *Kidney International* (2009) 75:1145-1152), the bleomycin induced model of pulmonary fibrosis (see Moore and Hogaboam, *Am. J. Physiol. Lung. Cell. Mol. Physiol.* (2008) 294:L152-L160), a variety of liver/biliary fibrosis models (see Chuang et al., *Clin Liver Dis* (2008) 12:333-347 and Omenetti, A. et al. (2007) *Laboratory Investigation* 87:499-514 (biliary duct-ligated model)), or a number of myelofibrosis mouse models (see Varicchio, L. et al. (2009) *Expert Rev. Hematol.* 2(3):315-334); efficacy in treating, preventing and/or managing scleroderma can be assessed using mouse model induced by repeated local injections of bleomycin ("BLM") described, for example, in Yamamoto et al. (1999) *J Invest Dermatol* 112: 456-462; efficacy in treating, preventing and/or managing dermatomyositis can be assessed using myositis mouse model induced by immunization with rabbit myosin described, for example, in Phyanagi et al. (2009) *Arthritis & Rheumatism,* 60(10): 3118-3127; efficacy in treating, preventing and/or managing lupus (e.g., CLE or SLE) can be assessed using various animal models described, for example, in Ghoreishi et al. (2009) *Lupus,* 19: 1029-1035, Ohl et al. (2011) *Journal of Biomedicine and Biotechnology*, Article ID

432595 (14 pages), Xia et al. (2011) *Rheumatology,* 50:2187-2196, Pau et al. (2012) *PLoS ONE,* 7(5):e36761 (15 pages), Mustafa et al. (2011) *Toxicology,* 290:156-168, Ichikawa et al. (2012) *Arthritis and Rheumatism,* 62(2): 493-503, Ouyang et al. (2012) *J Mol Med*, DOI 10.1007/s00109-012-0866-3 (10 pages), Rankin et al. (2012) *Journal of Immunology,* 188:1656-1667; and efficacy in treating, preventing and/or managing Sjögren's syndrome can be assessed using various mouse models described, for example, in Chiorini et al. (2009) *Journal of Autoimmunity,* 33: 190-196.

In one embodiment, provided herein is a method of treating, preventing and/or managing asthma. As used herein, "asthma" encompasses airway constriction regardless of the cause. Common triggers of asthma include, but are not limited to, exposure to an environmental stimulants (e.g., allergens), cold air, warm air, perfume, moist air, exercise or exertion, and emotional stress. Also provided herein is a method of treating, preventing and/or managing one or more symptoms associated with asthma. Examples of the symptoms include, but are not limited to, severe coughing, airway constriction and mucus production.

In one embodiment, provided herein is a method of treating, preventing and/or managing arthritis. As used herein, "arthritis" encompasses all types and manifestations of arthritis. Examples include, but are not limited to, crystalline arthritis, osteoarthritis, psoriatic arthritis, gouty arthritis, reactive arthritis, rheumatoid arthritis and Reiter's arthritis. In one embodiment, the disease or disorder is rheumatoid arthritis. In another embodiment, the disease or disorder is psoriatic arthritis. Also provided herein is a method of treating, preventing and/or managing one or more symptoms associated with arthritis. Examples of the symptoms include, but are not limited to, joint pain, which progresses into joint deformation, or damages in body organs such as in blood vessels, heart, lungs, skin, and muscles.

In one embodiment, provided herein is a method of treating, preventing and/or managing psoriasis. As used herein, "psoriasis" encompasses all types and manifestations of psoriasis. Examples include, but are not limited to, plaque psoriasis (e.g., chronic plaque psoriasis, moderate plaque psoriasis and severe plaque psoriasis), guttate psoriasis, inverse psoriasis, pustular psoriasis, pemphigus vulgaris, erythrodermic psoriasis, psoriasis associated with inflammatory bowel disease (IBD), and psoriasis associated with rheumatoid arthritis (RA). Also provided herein is a method of treating, preventing and/or managing one or more symptoms associated with psoriasis. Examples of the symptoms include, but are not limited to: red patches of skin covered with silvery scales; small scaling spots; dry, cracked skin that may bleed; itching; burning; soreness; thickened, pitted or ridged nails; and swollen and stiff joints.

In one embodiment, provided herein is a method of treating, preventing and/or managing fibrosis and fibrotic condition. As used herein, "fibrosis" or "fibrotic condition encompasses all types and manifestations of fibrosis or fibrotic condition. Examples include, but are not limited to, formation or deposition of tissue fibrosis; reducing the size, cellularity (e.g., fibroblast or immune cell numbers), composition; or cellular content, of a fibrotic lesion; reducing the collagen or hydroxyproline content, of a fibrotic lesion; reducing expression or activity of a fibrogenic protein; reducing fibrosis associated with an inflammatory response; decreasing weight loss associated with fibrosis; or increasing survival.

In certain embodiments, the fibrotic condition is primary fibrosis. In one embodiment, the fibrotic condition is idiopathic. In other embodiments, the fibrotic condition is associated with (e.g., is secondary to) a disease (e.g., an infectious disease, an inflammatory disease, an autoimmune disease, a malignant or cancerous disease, and/or a connective disease); a toxin; an insult (e.g., an environmental hazard (e.g., asbestos, coal dust, polycyclic aromatic hydrocarbons), cigarette smoking, a wound); a medical treatment (e.g., surgical incision, chemotherapy or radiation), or a combination thereof.

In some embodiments, the fibrotic condition is associated with an autoimmune disease selected from scleroderma or lupus, e.g., systemic lupus erythematosus. In some embodiments, the fibrotic condition is systemic. In some embodiments, the fibrotic condition is systemic sclerosis (e.g., limited systemic sclerosis, diffuse systemic sclerosis, or systemic sclerosis sine scleroderma), nephrogenic systemic fibrosis, cystic fibrosis, chronic graft vs. host disease, or atherosclerosis.

In certain embodiments, the fibrotic condition is a fibrotic condition of the lung, a fibrotic condition of the liver, a fibrotic condition of the heart or vasculature, a fibrotic condition of the kidney, a fibrotic condition of the skin, a fibrotic condition of the gastrointestinal tract, a fibrotic condition of the bone marrow or a hematopoietic tissue, a fibrotic condition of the nervous system, a fibrotic condition of the eye, or a combination thereof.

In other embodiment, the fibrotic condition affects a tissue chosen from one or more of muscle, tendon, cartilage, skin (e.g., skin epidermis or endodermis), cardiac tissue, vascular tissue (e.g., artery, vein), pancreatic tissue, lung tissue, liver tissue, kidney tissue, uterine tissue, ovarian tissue, neural tissue, testicular tissue, peritoneal tissue, colon, small intestine, biliary tract, gut, bone marrow, hematopoietic tissue, or eye (e.g., retinal) tissue.

In some embodiments, the fibrotic condition is a fibrotic condition of the eye. In some embodiments, the fibrotic condition is glaucoma, macular degeneration (e.g., age-related macular degeneration), macular edema (e.g., diabetic macular edema), retinopathy (e.g., diabetic retinopathy), or dry eye disease.

In certain embodiments, the fibrotic condition is a fibrotic condition of the lung. In certain embodiments, the fibrotic condition of the lung is chosen from one or more of: pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), usual interstitial pneumonitis (UIP), interstitial lung disease, cryptogenic fibrosing alveolitis (CFA), bronchiectasis, and scleroderma lung disease. In one embodiment, the fibrosis of the lung is secondary to a disease, a toxin, an insult, a medical treatment, or a combination thereof. For example, the fibrosis of the lung can be associated with (e.g., secondary to) one or more of: a disease process such as asbestosis and silicosis; an occupational hazard; an environmental pollutant; cigarette smoking; an autoimmune connective tissue disorders (e.g., rheumatoid arthritis, scleroderma and systemic lupus erythematosus (SLE)); a connective tissue disorder such as sarcoidosis; an infectious disease, e.g., infection, particularly chronic infection; a medical treatment, including but not limited to, radiation therapy, and drug therapy, e.g., chemotherapy (e.g., treatment with as bleomycin, methotrexate, amiodarone, busulfan, and/or nitrofurantoin). In one embodiment, the fibrotic condition of the lung treated with the methods provided herein is associated with (e.g., secondary to) a cancer treatment, e.g., treatment of a cancer (e.g., squamous cell carcinoma, testicular cancer, Hodgkin's disease with bleomycin). In one embodiment, the fibrotic condition of the lung is associated with an autoimmune connective tissue disorder (e.g., scleroderma or lupus, e.g., SLE).

In certain embodiments, the fibrotic condition is a fibrotic condition of the liver. In certain embodiments, the fibrotic condition of the liver is chosen from one or more of: fatty liver

disease, steatosis (e.g., nonalcoholic steatohepatitis (NASH), cholestatic liver disease (e.g., primary biliary cirrhosis (PBC)), cirrhosis, alcohol induced liver fibrosis, biliary duct injury, biliary fibrosis, or cholangiopathies. In other embodiments, hepatic or liver fibrosis includes, but is not limited to, hepatic fibrosis associated with alcoholism, viral infection, e.g., hepatitis (e.g., hepatitis C, B or D), autoimmune hepatitis, non-alcoholic fatty liver disease (NAFLD), progressive massive fibrosis, exposure to toxins or irritants (e.g., alcohol, pharmaceutical drugs and environmental toxins).

In certain embodiments, the fibrotic condition is a fibrotic condition of the heart. In certain embodiments, the fibrotic condition of the heart is myocardial fibrosis (e.g., myocardial fibrosis associated with radiation myocarditis, a surgical procedure complication (e.g., myocardial post-operative fibrosis), infectious diseases (e.g., Chagas disease, bacterial, trichinosis or fungal myocarditis)); granulomatous, metabolic storage disorders (e.g., cardiomyopathy, hemochromatosis); developmental disorders (e.g., endocardial fibroelastosis); arteriosclerotic, or exposure to toxins or irritants (e.g., drug induced cardiomyopathy, drug induced cardiotoxicity, alcoholic cardiomyopathy, cobalt poisoning or exposure). In certain embodiments, the myocardial fibrosis is associated with an inflammatory disorder of cardiac tissue (e.g., myocardial sarcoidosis). In some embodiments, the fibrotic condition is a fibrotic condition associated with a myocardial infarction. In some embodiments, the fibrotic condition is a fibrotic condition associated with congestive heart failure.

In certain embodiments, the fibrotic condition is a fibrotic condition of the kidney. In certain embodiments, the fibrotic condition of the kidney is chosen from one or more of: renal fibrosis (e.g., chronic kidney fibrosis), nephropathies associated with injury/fibrosis (e.g., chronic nephropathies associated with diabetes (e.g., diabetic nephropathy)), lupus, scleroderma of the kidney, glomerular nephritis, focal segmental glomerular sclerosis, IgA nephropathyrenal fibrosis associated with human chronic kidney disease (CKD), chronic progressive nephropathy (CPN), tubulointerstitial fibrosis, ureteral obstruction, chronic uremia, chronic interstitial nephritis, radiation nephropathy, glomerulosclerosis, progressive glomerulonephrosis (PGN), endothelial/thrombotic microangiopathy injury, HIV-associated nephropathy, or fibrosis associated with exposure to a toxin, an irritant, or a chemotherapeutic agent. In one embodiment, the fibrotic condition of the kidney is scleroderma of the kidney. In some embodiments, the fibrotic condition of the kidney is transplant nephropathy, diabetic nephropathy, lupus nephritis, or focal segmental glomerulosclerosis (FSGS).

In certain embodiments, the fibrotic condition is a fibrotic condition of the skin. In certain embodiments, the fibrotic condition of the skin is chosen from one or more of: skin fibrosis (e.g., hypertrophic scarring, keloid), scleroderma, nephrogenic systemic fibrosis (e.g., resulting after exposure to gadolinium (which is frequently used as a contrast substance for MRIs) in patients with severe kidney failure), and keloid.

In certain embodiments, the fibrotic condition is a fibrotic condition of the gastrointestinal tract. In certain embodiments, the fibrotic condition is chosen from one or more of: fibrosis associated with scleroderma; radiation induced gut fibrosis; fibrosis associated with a foregut inflammatory disorder such as Barrett's esophagus and chronic gastritis, and/or fibrosis associated with a hindgut inflammatory disorder, such as inflammatory bowel disease (IBD), ulcerative colitis and Crohn's disease. In some embodiments, the fibrotic condition of the gastrointestinal tract is fibrosis associated with scleroderma.

In certain embodiments, the fibrotic condition is a fibrotic condition of the bone marrow or a hematopoietic tissue. In certain embodiments, the fibrotic condition of the bone marrow is an intrinsic feature of a chronic myeloproliferative neoplasm of the bone marrow, such as primary myelofibrosis (also referred to herein as agnogenic myeloid metaplasia or chronic idiopathic myelofibrosis). In other embodiments, the bone marrow fibrosis is associated with (e.g., is secondary to) a malignant condition or a condition caused by a clonal proliferative disease. In other embodiments, the bone marrow fibrosis is associated with a hematologic disorder (e.g., a hematologic disorder chosen from one or more of polycythemia vera, essential thrombocythemia, myelodysplasia, hairy cell leukemia, lymphoma (e.g., Hodgkin or non-Hodgkin lymphoma), multiple myeloma or chronic myelogeneous leukemia (CML)). In yet other embodiments, the bone marrow fibrosis is associated with (e.g., secondary to) a non-hematologic disorder (e.g., a non-hematologic disorder chosen from solid tumor metastasis to bone marrow, an autoimmune disorder (e.g., systemic lupus erythematosus, scleroderma, mixed connective tissue disorder, or polymyositis), an infection (e.g., tuberculosis), or secondary hyperparathyroidism associated with vitamin D deficiency. In some embodiments, the fibrotic condition is idiopathic or drug-induced myelofibrosis. In some embodiments, the fibrotic condition of the bone marrow or hematopoietic tissue is associated with systemic lupus erythematosus or scleroderma.

In one embodiment, provided herein is a method of treating, preventing and/or managing scleroderma. Scleroderma is a group of diseases that involve hardening and tightening of the skin and/or other connective tissues. Scleroderma may be localized (e.g., affecting only the skin) or systemic (e.g., affecting other systems such as, e.g., blood vessels and/or internal organs). Common symptoms of scleroderma include Raynaud's phenomenon, gastroesophageal reflux disease, and skin changes (e.g., swollen fingers and hands, or thickened patches of skin). In some embodiments, the scleroderma is localized, e.g., morphea or linear scleroderma. In some embodiments, the condition is a systemic sclerosis, e.g., limited systemic sclerosis, diffuse systemic sclerosis, or systemic sclerosis sine scleroderma.

Localized scleroderma (localized cutaneous fibrosis) includes morphea and linear scleroderma. Morphea is typically characterized by oval-shaped thickened patches of skin that are white in the middle, with a purple border. Linear scleroderma is more common in children. Symptoms of linear scleroderma may appear mostly on one side of the body. In linear scleroderma, bands or streaks of hardened skin may develop on one or both arms or legs or on the forehead. En coup de sabre (frontal linear scleroderma or morphea en coup de sabre) is a type of localized scleroderma typically characterized by linear lesions of the scalp or face.

Systemic scleroderma (systemic sclerosis) includes, e.g., limited systemic sclerosis (also known as limited cutaneous systemic sclerosis, or CREST syndrome), diffuse systemic sclerosis (also known as diffuse cutaneous systemic sclerosis), and systemic sclerosis sine scleroderma. CREST stands for the following complications that may accompany limited scleroderma: calcinosis (e.g., of the digits), Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasias. Typically, limited scleroderma involves cutaneous manifestations that mainly affect the hands, arms, and face. Limited and diffuse subtypes are distinguished based on the extent of skin involvement, with sparing of the proximal limbs and trunk in limited disease. See, e.g., Denton, C. P. et al. (2006), *Nature Clinical Practice Rheumatology,* 2(3):134-143. The limited subtype also typically involves a long pre-

vious history of Raynaud's phenomenon, whereas in the diffuse subtype, onset of Raynaud's phenomenon can be simultaneous with other manifestations or might occur later. Both limited and diffuse subtypes may involve internal organs. Typical visceral manifestations of limited systemic sclerosis include isolated pulmonary hypertension, severe bowel involvement, and pulmonary fibrosis. Typical visceral manifestations of diffuse systemic sclerosis include renal crisis, lung fibrosis, and cardiac disease. Diffuse systemic sclerosis typically progresses rapidly and affects a large area of the skin and one or more internal organs (e.g., kidneys, esophagus, heart, or lungs). Systemic sclerosis sine scleroderma is a rare disorder in which patients develop vascular and fibrotic damage to internal organs in the absence of cutaneous sclerosis.

In one embodiment, provided herein is a method of treating, preventing and/or managing inflammatory myopathies. As used herein, "inflammatory myopathies" encompass all types and manifestations of inflammatory myopathies. Examples include, but are not limited to, muscle weakness (e.g., proximal muscle weakness), skin rash, fatigue after walking or standing, tripping or falling, dysphagia, dysphonia, difficulty breathing, muscle pain, tender muscles, weight loss, low-grade fever, inflamed lungs, light sensitivity, calcium deposits (calcinosis) under the skin or in the muscle, as well as biological concomitants of inflammatory myopathies as disclosed herein or as known in the art. Biological concomitants of inflammatory myopathies (e.g., dermatomyositis) include, e.g., altered (e.g., increased) levels of cytokines (e.g., Type I interferons (e.g., IFN-α and/or IFN-β), interleukins (e.g., IL-6, IL-10, IL-15, IL-17 and IL-18), and TNF-α), TGF-β, B-cell activating factor (BAFF), overexpression of IFN inducible genes (e.g., Type I IFN inducible genes). Other biological concomitants of inflammatory myopathies can include, e.g., an increased erythrocyte sedimentation rate (ESR) and/or elevated level of creatine kinase. Further biological concomitants of inflammatory myopathies can include autoantibodies, e.g., anti-synthetase autoantibodies (e.g., anti-Jo1 antibodies), anti-signal recognition particle antibodies (anti-SRP), anti-Mi-2 antibodies, anti-p155 antibodies, anti-PM/Sci antibodies, and anti-RNP antibodies.

The inflammatory myopathy can be an acute inflammatory myopathy or a chronic inflammatory myopathy. In some embodiments, the inflammatory myopathy is a chronic inflammatory myopathy (e.g., dermatomyositis, polymyositis, or inclusion body myositis). In some embodiments, the inflammatory myopathy is caused by an allergic reaction, another disease (e.g., cancer or a connective tissue disease), exposure to a toxic substance, a medicine, or an infectious agent (e.g., a virus). In some embodiments, the inflammatory myopathy is associated with lupus, rheumatoid arthritis, or systemic sclerosis. In some embodiments, the inflammatory myopathy is idiopathic. In some embodiments, the inflammatory myopathy is selected from polymyositis, dermatomyositis, inclusion body myositis, and immune-mediated necrotizing myopathy. In some embodiments, the inflammatory myopathy is dermatomyositis.

In another embodiment, provided herein is a method of treating, preventing and/or managing a skin condition (e.g., a dermatitis). In some embodiments, the methods provided herein can reduce symptoms associated with a skin condition (e.g., itchiness and/or inflammation). In some such embodiments, the compound provided herein is administered topically (e.g., as a topical cream, eye-drop, nose drop or nasal spray). In some such embodiments, the compound is a PI3K delta inhibitor (e.g., a PI3K inhibitor that demonstrates greater inhibition of PI3K delta than of other PI3K isoforms). In some embodiments, the PI3K delta inhibitor prevents mast cell degranulation.

As used herein, "skin condition" includes any inflammatory condition of the skin (e.g., eczema or dermatitis, e.g., contact dermatitis, atopic dermatitis, dermatitis herpetiformis, seborrheic dermatitis, nummular dermatitis, stasis dermatitis, perioral dermatitis), as well as accompanying symptoms (e.g., skin rash, itchiness (pruritis), swelling (edema), hay fever, anaphalaxis). Frequently, such skin conditions are caused by an allergen. As used herein, a "skin condition" also includes, e.g., skin rashes (e.g., allergic rashes, e.g., rashes resulting from exposure to allergens such as poison ivy, poison oak, or poison sumac, or rashes caused by other diseases or conditions), insect bites, minor burns, sunburn, minor cuts, and scrapes. In some embodiments, the symptom associated with inflammatory myopathy, or the skin condition or symptom associated with the skin condition, is a skin rash or itchiness (pruritis) caused by a skin rash.

The skin condition (e.g., the skin rash) may be spontaneous, or it may be induced, e.g., by exposure to an allergen (e.g., poison ivy, poison oak, or poison sumac), drugs, food, insect bite, inhalants, emotional stress, exposure to heat, exposure to cold, or exercise. In some embodiments, the skin condition is a skin rash (e.g., a pruritic rash, e.g., utricaria). In some embodiments, the skin condition is an insect bite. In some embodiments, the skin condition is associated with another disease (e.g., an inflammatory myopathy, e.g., dermatomyositis).

In some embodiments, the subject (e.g., the subject in need of treatment for an inflammatory myopathy and/or a skin condition) exhibits an elevated level or elevated activity of IFN-α, TNF-α, IL-6, IL-8, IL-1, or a combination thereof. In certain embodiments, the subject exhibits an elevated level of IFN-α. In some embodiments, treating (e.g., decreasing or inhibiting) the inflammatory myopathy, or the skin condition, comprises inhibiting (e.g., decreasing a level of, or decreasing a biological activity of) one or more of IFN-α, TNF-α, IL-6, IL-8, or IL-1 in the subject or in a sample derived from the subject. In some embodiments, the method decreases a level of IFN-α, TNF-α, IL-6, IL-8, or IL-1 in the subject or in a sample derived from the subject. In some embodiments, the method decreases a level of IFN-α in the subject or in a sample derived from the subject. In some embodiments, the level of IFN-α, TNF-α, IL-6, IL-8, or IL-1 is the level assessed in a sample of whole blood or PBMCs. In some embodiments, the level of IFN-α, TNF-α, IL-6, IL-8, or IL-1 is the level assessed in a sample obtained by a skin biopsy or a muscle biopsy. In some embodiments, the sample is obtained by a skin biopsy.

In one embodiment, provided herein is a method of treating, preventing and/or managing myositis. As used herein, "myositis" encompasses all types and manifestations of myositis. Examples include, but are not limited to, myositis ossificans, fibromyositis, idiopathic inflammatory myopathies, dermatomyositis, juvenile dermatomyositis, polymyositis, inclusion body myositis and pyomyositis. In one embodiment, the disease or disorder is dermatomyositis. Also provided herein is a method of treating, preventing and/or managing one or more symptoms associated with myositis. Examples of the symptoms include, but are not limited to: muscle weakness; trouble lifting arms; trouble swallowing or breathing; muscle pain; muscle tenderness; fatigue; fever; lung problems; gastrointestinal ulcers; intestinal perforations; calcinosis under the skin; soreness; arthritis; weight loss; and rashes.

In one embodiment, provided herein is a method of treating, preventing and/or managing lupus. As used herein, "lupus" refers to all types and manifestations of lupus. Examples include, but are not limited to, systemic lupus erythematosus; lupus nephritis; cutaneous manifestations (e.g., manifestations seen in cutaneous lupus erythematosus, e.g., a skin lesion or rash); CNS lupus; cardiovascular, pulmonary, hepatic, hematological, gastrointestinal and musculoskeletal manifestations; neonatal lupus erythematosus; childhood systemic lupus erythematosus; drug-induced lupus erythematosus; anti-phospholipid syndrome; and complement deficiency syndromes resulting in lupus manifestations. In one embodiment, the lupus is systemic lupus erythematosus (SLE), cutaneous lupus erythematosus (CLE), drug-induced lupus, or neonatal lupus. In another embodiment, the lupus is a CLE, e.g., acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), intermittent cutaneous lupus erythematosus (also known as lupus erythematosus tumidus (LET)), or chronic cutaneous lupus. In some embodiments, the intermittent CLE is chronic discloid lupus erythematosus (CDLE) or lupus erythematosus profundus (LEP) (also known as lupus erythematosus panniculitis). Types, symptoms, and pathogenesis of CLE are described, for example, in Wenzel et al. (2010), *Lupus,* 19, 1020-1028.

In one embodiment, provided herein is a method of treating, preventing and/or managing Sjögren's syndrome. As used herein, "Sjögren's syndrome" refers to all types and manifestations of Sjögren's syndrome. Examples include, but are not limited to, primary and secondary Sjögren's syndrome. Also provided herein is a method of treating, preventing and/or managing one or more symptoms associated with Sjögren's syndrome. Examples of the symptoms include, but are not limited to: dry eyes; dry mouth; joint pain; swelling; stiffness; swollen salivary glands; skin rashes; dry skin; vaginal dryness; persistent dry cough; and prolonged fatigue.

In some embodiments, a symptom associated with the disease or disorder provided herein is reduced by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% relative to a control level. The control level includes any appropriate control as known in the art. For example, the control level can be the pre-treatment level in the sample or subject treated, or it can be the level in a control population (e.g., the level in subjects who do not have the disease or disorder or the level in samples derived from subjects who do not have the disease or disorder). In some embodiments, the decrease is statistically significant, for example, as assessed using an appropriate parametric or non-parametric statistical comparison.

Combination Therapy

In some embodiments, provided herein are methods for combination therapies in which an agent known to modulate other pathways, or other components of the same pathway, or even overlapping sets of target enzymes are used in combination with a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof. In one aspect, such therapy includes, but is not limited to, the combination of the subject compound with chemotherapeutic agents, therapeutic antibodies, and radiation treatment, to provide a synergistic or additive therapeutic effect.

By "in combination with," it is not intended to imply that the other therapy and the PI3K modulator must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope of this disclosure. The compound provided herein can be administered concurrently with, prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, 12 weeks, or 16 weeks before), or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, 12 weeks, or 16 weeks after), one or more other therapies (e.g., one or more other additional agents). In general, each therapeutic agent will be administered at a dose and/or on a time schedule determined for that particular agent. The other therapeutic agent can be administered with the compound provided herein in a single composition or separately in a different composition. Triple therapy is also contemplated herein.

In general, it is expected that additional therapeutic agents employed in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

In some embodiments, the compound provided herein is a first line treatment for cancer or hematologic malignancy, i.e., it is used in a subject who has not been previously administered another drug or therapy intended to treat cancer or hematologic malignancy or one or more symptoms thereof.

In other embodiments, the compound provided herein is a second line treatment for cancer or hematologic malignancy, i.e., it is used in a subject who has been previously administered another drug or therapy intended to treat cancer or hematologic malignancy or one or more symptoms thereof.

In other embodiments, the compound provided herein is a third or fourth line treatment for cancer or hematologic malignancy, i.e., it is used in a subject who has been previously administered two or three other drugs or therapies intended to treat cancer or hematologic malignancy or one or more symptoms thereof.

In embodiments where two agents are administered, the agents can be administered in any order. For example, the two agents can be administered concurrently (i.e., essentially at the same time, or within the same treatment) or sequentially (i.e., one immediately following the other, or alternatively, with a gap in between administration of the two). In some embodiments, the compound provided herein is administered sequentially (i.e., after the first therapeutic).

In one aspect, a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, can present synergistic or additive efficacy when administered in combination with agents that inhibit IgE production or activity. Such combination can reduce the undesired effect of high level of IgE associated with the use of one or more PI3K-δ inhibitors, if such effect occurs. This can be particularly useful in treatment of autoimmune and inflammatory disorders (AIID) such as rheumatoid arthritis. Additionally, the administration of PI3K-δ, PI3K-γ, or PI3K-δ/γ inhibitors as provided herein in combination with inhibitors of mTOR can also exhibit synergy through enhanced inhibition of the PI3K pathway.

In a separate but related aspect, provided herein is a combination treatment of a disease associated with PI3K-δ comprising administering to a subject in need thereof a PI3K-δ inhibitor and an agent that inhibits IgE production or activity. Other exemplary PI3K-δ inhibitors are applicable for this combination and they are described in, e.g., U.S. Pat. No.

6,800,620, incorporated herein by reference. Such combination treatment is particularly useful for treating autoimmune and inflammatory diseases (AIID) including, but not limited to rheumatoid arthritis.

Agents that inhibit IgE production are known in the art and they include, but are not limited to, one or more of TEI-9874, 2-(4-(6-cyclohexyloxy-2-naphtyloxy)phenylacetamide)benzoic acid, rapamycin, rapamycin analogs (i.e., rapalogs), TORC1 inhibitors, TORC2 inhibitors, and any other compounds that inhibit mTORC1 and mTORC2. Agents that inhibit IgE activity include, for example, anti-IgE antibodies such as for example Omalizumab and TNX-901.

For treatment of autoimmune diseases, a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, can be used in combination with commonly prescribed drugs including, but not limited to, Enbrel®, Remicade®, Humira®, Avonex®, and Rebif®. For treatment of respiratory diseases, the subject compounds, or pharmaceutically acceptable forms thereof, or pharmaceutical compositions, can be administered in combination with commonly prescribed drugs including, but not limited to, Xolair®, Advair®, Singulair®, and Spiriva®.

The compounds as provided herein, or pharmaceutically acceptable forms (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, can be formulated or administered in conjunction with other agents that act to relieve the symptoms of inflammatory conditions such as encephalomyelitis, asthma, and the other diseases described herein. These agents include non-steroidal anti-inflammatory drugs (NSAIDs), e.g., acetylsalicylic acid; ibuprofen; naproxen; indomethacin; nabumetone; tolmetin; etc. Corticosteroids are used to reduce inflammation and suppress activity of the immune system. An exemplary drug of this type is Prednisone. Chloroquine (Aralen) or hydroxychloroquine (Plaquenil) can also be used in some individuals with lupus. They can be prescribed for skin and joint symptoms of lupus. Azathioprine (Imuran) and cyclophosphamide (Cytoxan) suppress inflammation and tend to suppress the immune system. Other agents, e.g., methotrexate and cyclosporin are used to control the symptoms of lupus. Anticoagulants are employed to prevent blood from clotting rapidly. They range from aspirin at very low dose which prevents platelets from sticking, to heparin/coumadin. Other compounds used in the treatment of lupus include belimumab (Benlysta®).

In another aspect, provided herein is a pharmaceutical composition for inhibiting abnormal cell growth in a subject which comprises an amount of a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, in combination with an amount of an anti-cancer agent (e.g., a chemotherapeutic agent). Many chemotherapeutics are presently known in the art and can be used in combination with a compound provided herein.

In some embodiments, the chemotherapeutic is selected from mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens. Non-limiting examples are chemotherapeutic agents, cytotoxic agents, and non-peptide small molecules such as Gleevec® (imatinib mesylate), Velcade® (bortezomib), Casodex™ (bicalutamide), Iressa® (gefitinib), Tarceva® (erlotinib), and Adriamycin® (doxorubicin) as well as a host of chemotherapeutic agents. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide (CYTOXAN™); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine; BTK inhibitors such as ibrutinib (PCI-32765), AVL-292, Dasatinib, LFM-AI3, ONO-WG-307, and GDC-0834; HDAC inhibitors such as vorinostat, romidepsin, panobinostat, valproic acid, belinostat, mocetinostat, abrexinostat, entinostat, SB939, resminostat, givinostat, CUDC-101, AR-42, CHR-2845, CHR-3996, 4SC-202, CG200745, ACY-1215 and kevetrin; EZH2 inhibitors such as, but not limited to, EPZ-6438 (N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide), GSK-126 ((S)-1-(sec-butyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-methyl-6-(6-(piperazin-1-yl)pyridin-3-yl)-1H-indole-4-carboxamide), GSK-343 (1-Isopropyl-N-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-6-(2-(4-methylpiperazin-1-yl)pyridine-4-yl)-1H-indazole-4-carboxamide), El1, 3-deazaneplanocin A (DNNep, 5R-(4-amino-1H-imidazo[4,5-c]pyridin-1-yl)-3-(hydroxymethyl)-3-cyclopentene-1 S,2R-diol), small interfering RNA (siRNA) duplexes targeted against EZH2 (S. M. Elbashir et al., Nature 411:494-498 (2001)), isoliquiritigenin, and those provided in, for example, U.S. Publication Nos. 2009/0012031, 2009/0203010, 2010/0222420, 2011/0251216, 2011/0286990, 2012/0014962, 2012/0071418, 2013/0040906, and 2013/0195843, all of which are incorporated herein by reference; JAK/STAT inhibitors such as lestaurtinib, tofacitinib, ruxolitinib, pacritinib, CYT387, baricitinib, GLPG0636, TG101348, INCB16562, CP-690550, and AZD1480; PKC-β inhibitor such as Enzastaurin; SYK inhibitors such as, but not limited to, GS-9973, R788 (fostamatinib), PRT 062607, R406, (S)-2-(2-((3,5-dimethylphenyl)amino)pyrimidin-4-yl)-N-(1-hydroxypropan-2-yl)-4-methylthiazole-5-carboxamide, R112, GSK143, BAY61-3606, PP2, PRT 060318, R348, and those provided in, for example, U.S. Publication Nos. 2003/0113828, 2003/0158195, 2003/0229090, 2005/0075306, 2005/0232969, 2005/0267059, 2006/0205731, 2006/0247262, 2007/0219152, 2007/0219195, 2008/0114024, 2009/0171089, 2009/0306214, 2010/0048567, 2010/0152159, 2010/0152182, 2010/0316649, 2011/0053897, 2011/0112098, 2011/0245205, 2011/0275655, 2012/0027834, 2012/0093913, 2012/0101275, 2012/0130073, 2012/0142671, 2012/0184526, 2012/0220582, 2012/0277192, 2012/0309735, 2013/0040984, 2013/0090309, 2013/0116260, and 2013/0165431, all of which are incorporated herein by reference; SYK/JAK dual inhibitor such as PRT2070; nitrogen mustards such as bendamustine, chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomycins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycin C, myco-

phenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pralatrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as folinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatrexate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK.R™; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethyla-mine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside (Ara-C); cyclophosphamide; thiotepa; taxanes, e.g., paclitaxel (e.g., TAXOL™) and docetaxel (e.g., TAXOTERE™) and ABRAXANE® (paclitaxel protein-bound particles); retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable forms (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) of any of the above. Also included as suitable chemotherapeutic cell conditioners are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen (Nolvadex™), raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; camptothecin-11 (CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO). Where desired, the compounds or pharmaceutical composition as provided herein can be used in combination with commonly prescribed anti-cancer drugs such as Herceptin®, Avastin®, Erbitux®, Rituxan®, Taxol®, Arimidex®, Taxotere®, ABVD, AVICINE, abagovomab, acridine carboxamide, adecatumumab, 17-N-allylamino-17-demethoxygeldanamycin, alpharadin, alvocidib, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone, amonafide, anthracenedione, anti-CD22 immunotoxins, antineoplastic, antitumorigenic herbs, apaziquone, atiprimod, azathioprine, belotecan, bendamustine, BIBW 2992, biricodar, brostallicin, bryostatin, buthionine sulfoximine, CBV (chemotherapy), calyculin, crizotinib, cell-cycle nonspecific antineoplastic agents, dichloroacetic acid, discodermolide, elsamitrucin, enocitabine, epothilone, eribulin, everolimus, exatecan, exisulind, ferruginol, forodesine, fosfestrol, ICE chemotherapy regimen, IT-101, imexon, imiquimod, indolocarbazole, irofulven, laniquidar, larotaxel, lenalidomide, lucanthone, lurtotecan, mafosfamide, mitozolomide, nafoxidine, nedaplatin, olaparib, ortataxel, PAC-1, pawpaw, pixantrone, proteasome inhibitor, rebeccamycin, resiquimod, rubitecan, SN-38, salinosporamide A, sapacitabine, Stanford V, swainsonine, talaporfin, tariquidar, tegafur-uracil, temodar, tesetaxel, triplatin tetranitrate, tris(2-chloroethyl)amine, troxacitabine, uramustine, vadimezan, vinflunine, ZD6126, and zosuquidar.

In some embodiments, the chemotherapeutic is selected from hedgehog inhibitors including, but not limited to IPI-926 (See U.S. Pat. No. 7,812,164). Other suitable hedgehog inhibitors include, for example, those described and disclosed in U.S. Pat. No. 7,230,004, U.S. Patent Application Publication No. 2008/0293754, U.S. Patent Application Publication No. 2008/0287420, and U.S. Patent Application Publication No. 2008/0293755, the entire disclosures of which are incorporated by reference herein. Examples of other suitable hedgehog inhibitors include those described in U.S. Patent Application Publication Nos. US 2002/0006931, US 2007/0021493 and US 2007/0060546, and International Application Publication Nos. WO 2001/19800, WO 2001/26644, WO 2001/27135, WO 2001/49279, WO 2001/74344, WO 2003/011219, WO 2003/088970, WO 2004/020599, WO 2005/013800, WO 2005/033288, WO 2005/032343, WO 2005/042700, WO 2006/028958, WO 2006/050351, WO 2006/078283, WO 2007/054623, WO 2007/059157, WO 2007/120827, WO 2007/131201, WO 2008/070357, WO 2008/110611, WO 2008/112913, and WO 2008/131354, each incorporated herein by reference. Additional examples of hedgehog inhibitors include, but are not limited to, GDC-0449 (also known as RG3616 or vismodegib) described in, e.g., Von Hoff D. et al., *N. Engl. J. Med.* 2009; 361(12):1164-72; Robarge K. D. et al., *Bioorg Med Chem Lett.* 2009; 19(19):5576-81; Yauch, R. L. et al. (2009) *Science* 326: 572-574; Sciencexpress: 1-3 (10.1126/science.1179386); Rudin, C. et al. (2009) *New England J of Medicine* 361-366 (10.1056/nejma0902903); BMS-833923 (also known as XL139) described in, e.g., in Siu L. et al., *J. Clin. Oncol.* 2010; 28:15s (suppl; abstr 2501); and National Institute of Health Clinical Trial Identifier No. NCT006701891; LDE-225 described, e.g., in Pan S. et al., *ACS Med. Chem. Lett.,* 2010; 1(3): 130-134; LEQ-506 described, e.g., in National Institute of Health Clinical Trial Identifier No. NCT01106508; PF-04449913 described, e.g., in National Institute of Health Clinical Trial Identifier No. NCT00953758; Hedgehog pathway antagonists disclosed in U.S. Patent Application Publication No. 2010/0286114; SMOi2-17 described, e.g., U.S. Patent Application Publication No. 2010/0093625; SANT-1 and SANT-2 described, e.g., in Rominger C. M. et al., *J. Pharmacol. Exp. Ther.* 2009; 329(3):995-1005; 1-piperazinyl-4-arylphthalazines or analogues thereof, described in Lucas B. S. et al., *Bioorg. Med. Chem. Lett.* 2010; 20(12):3618-22.

Other hormonal therapy and chemotherapeutic agents include, but are not limited to, anti-estrogens (e.g. tamoxifen, raloxifene, and megestrol acetate), LHRH agonists (e.g. goserelin and leuprolide), anti-androgens (e.g. flutamide and bicalutamide), photodynamic therapies (e.g. vertoporfin (BPD-MA), phthalocyanine, photosensitizer Pc4, and demethoxy-hypocrellin A (2BA-2-DMHA)), nitrogen mustards (e.g. cyclophosphamide, ifosfamide, trofosfamide, chlorambucil, estramustine, and melphalan), nitrosoureas (e.g. carmustine (BCNU) and lomustine (CCNU)), alkylsulphonates (e.g. busulfan and treosulfan), triazenes (e.g. dacarbazine, temozolomide), platinum containing compounds (e.g. cisplatin, carboplatin, oxaliplatin), vinca alkaloids (e.g. vincristine, vinblastine, vindesine, and vinorelbine), taxoids or taxanes (e.g. paclitaxel or a paclitaxel equivalent such as nanoparticle albumin-bound paclitaxel (Abraxane), docosahexaenoic acid bound-paclitaxel (DHA-paclitaxel, Taxoprexin), polyglutamate bound-paclitaxel (PG-paclitaxel,

paclitaxel poliglumex, CT-2103, XYOTAX), the tumor-activated prodrug (TAP) ANG1005 (Angiopep-2 bound to three molecules of paclitaxel), paclitaxel-EC-1 (paclitaxel bound to the erbB2-recognizing peptide EC-1), and glucose-conjugated paclitaxel, e.g., 2'-paclitaxel methyl 2-glucopyranosyl succinate; docetaxel, taxol), epipodophyllins (e.g. etoposide, etoposide phosphate, teniposide, topotecan, 9-aminocamptothecin, camptoirinotecan, irinotecan, crisnatol, mytomycin C), anti-metabolites, DHFR inhibitors (e.g. methotrexate, dichloromethotrexate, trimetrexate, edatrexate), IMP dehydrogenase inhibitors (e.g. mycophenolic acid, tiazofurin, ribavirin, and EICAR), ribonuclotide reductase inhibitors (e.g. hydroxyurea and deferoxamine), uracil analogs (e.g. 5-fluorouracil (5-FU), floxuridine, doxifluridine, raltitrexed, tegafur-uracil, capecitabine), cytosine analogs (e.g. cytarabine (ara C, cytosine arabinoside), and fludarabine), purine analogs (e.g. mercaptopurine and thioguanine), Vitamin D3 analogs (e.g. EB 1089, CB 1093, and KH 1060), isoprenylation inhibitors (e.g. lovastatin), dopaminergic neurotoxins (e.g. 1-methyl-4-phenylpyridinium ion), cell cycle inhibitors (e.g. staurosporine), actinomycin (e.g. actinomycin D, dactinomycin), bleomycin (e.g. bleomycin A2, bleomycin B2, peplomycin), anthracyclines (e.g. daunorubicin, doxorubicin, pegylated liposomal doxorubicin, idarubicin, epirubicin, pirarubicin, zorubicin, mitoxantrone), MDR inhibitors (e.g. verapamil), Ca2+ ATPase inhibitors (e.g. thapsigargin), thalidomide, lenalidomide (REVLIMID®), tyrosine kinase inhibitors (e.g., axitinib (AG013736), bosutinib (SKI-606), cediranib (RECENTIN™, AZD2171), dasatinib (SPRYCEL®, BMS-354825), erlotinib (TARCEVA®), gefitinib (IRESSA®), imatinib (Gleevec®, CGP57148B, STI-571), lapatinib (TYKERB®, TYVERB®), lestaurtinib (CEP-701), neratinib (HKI-272), nilotinib (TASIGNA®), semaxanib (semaxinib, SU5416), sunitinib (SUTENT®, SU11248), toceranib (PALLADIA®), vandetanib (ZACTIMA®, ZD6474), vatalanib (PTK787, PTK/ZK), trastuzumab (HERCEPTIN®), bevacizumab (AVASTIN®), rituximab (RITUXAN®), cetuximab (ERBITUX®), panitumumab (VECTIBIX®), ranibizumab (Lucentis®), sorafenib (NEXAVAR®), everolimus (AFINITOR®), alemtuzumab (CAMPATH®), gemtuzumab ozogamicin (MYLOTARG®), temsirolimus (TORISEL®), ENMD-2076, PCI-32765, AC220, dovitinib lactate (TKI258, CHIR-258), BIBW 2992 (TOVOK™), SGX523, PF-04217903, PF-02341066, PF-299804, BMS-777607, ABT-869, MP470, BIBF 1120 (VARGATEF®), AP24534, JNJ-26483327, MGCD265, DCC-2036, BMS-690154, CEP-11981, tivozanib (AV-951), OSI-930, MM-121, XL-184, XL-647, and/or XL228), proteasome inhibitors (e.g., bortezomib (Velcade)), mTOR inhibitors (e.g., rapamycin, temsirolimus (CCI-779), everolimus (RAD-001), ridaforolimus, AP23573 (Ariad), AZD8055 (AstraZeneca), BEZ235 (Novartis), BGT226 (Norvartis), XL765 (Sanofi Aventis), PF-4691502 (Pfizer), GDC0980 (Genetech), SF1126 (Semafoe) and OSI-027 (OSI)), oblimersen, gemcitabine, carminomycin, leucovorin, pemetrexed, cyclophosphamide, dacarbazine, procarbazine, prednisolone, dexamethasone, camptothecin, plicamycin, asparaginase, aminopterin, methopterin, porfiromycin, melphalan, leurosidine, leurosine, chlorambucil, trabectedin, procarbazine, discodermolide, carminomycin, aminopterin, and hexamethyl melamine.

Exemplary biotherapeutic agents include, but are not limited to, interferons, cytokines (e.g., tumor necrosis factor, interferon α, interferon γ), vaccines, hematopoietic growth factors, monoclonal serotherapy, immuno-stimulants and/or immuno-modulatory agents (e.g., IL-1, 2, 4, 6, or 12), immune cell growth factors (e.g., GM-CSF) and antibodies (e.g. Herceptin (trastuzumab), T-DM1, AVASTIN (bevacizumab), ERBITUX (cetuximab), Vectibix (panitumumab), Rituxan (rituximab), Bexxar (tositumomab), or Perjeta (pertuzumab)).

In one embodiment, the biotherapeutic agent is an anti-CD37 antibody such as, but not limited to, IMGN529, K7153A and TRU-016. In another embodiment, the biotherapeutic agent is an anti-CD20 antibody such as, but not limited to, ^{131}I tositumomab, ^{90}Y ibritumomab, ^{111}I ibritumomab, obinutuzumab and ofatumumab. In another embodiment, the biotherapeutic agent is an anti-CD52 antibody such as, but not limited to, alemtuzumab.

In some embodiments, the chemotherapeutic is selected from HSP90 inhibitors. The HSP90 inhibitor can be a geldanamycin derivative, e.g., a benzoquinone or hygroquinone ansamycin HSP90 inhibitor (e.g., IPI-493 and/or IPI-504). Non-limiting examples of HSP90 inhibitors include IPI-493, IPI-504, 17-AAG (also known as tanespimycin or CNF-1010), BIIB-021 (CNF-2024), BIIB-028, AUY-922 (also known as VER-49009), SNX-5422, STA-9090, AT-13387, XL-888, MPC-3100, CU-0305, 17-DMAG, CNF-1010, Macbecin (e.g., Macbecin I, Macbecin II), CCT-018159, CCT-129397, PU-H71, or PF-04928473 (SNX-2112).

In some embodiments, the chemotherapeutic is selected from PI3K inhibitors (e.g., including those PI3K inhibitors provided herein and those PI3K inhibitors not provided herein). In some embodiment, the PI3K inhibitor is an inhibitor of delta and gamma isoforms of PI3K. In some embodiment, the PI3K inhibitor is an inhibitor of delta isoform of PI3K. In some embodiment, the PI3K inhibitor is an inhibitor of gamma isoform of PI3K. In some embodiments, the PI3K inhibitor is an inhibitor of alpha isoform of PI3K. In other embodiments, the PI3K inhibitor is an inhibitor of one or more alpha, beta, delta and gamma isoforms of PI3K. Exemplary PI3K inhibitors that can be used in combination are described in, e.g., WO 09/088990, WO 09/088086, WO 2011/008302, WO 2010/036380, WO 2010/006086, WO 09/114870, WO 05/113556; US 2009/0312310, and US 2011/0046165, each incorporated herein by reference. Additional PI3K inhibitors that can be used in combination with the pharmaceutical compositions, include but are not limited to, AMG-319, GSK 2126458, GDC-0980, GDC-0941, Sanofi XL147, XL499, XL756, XL147, PF-4691502, BKM 120, CAL-101 (GS-1101), CAL 263, SF1126, PX-886, and a dual PI3K inhibitor (e.g., Novartis BEZ235). In one embodiment, the PI3K inhibitor is an isoquinolinone.

In one embodiment, the PI3K gamma selective compound selectively inhibits PI3K gamma isoform over PI3K delta isoform. In one embodiment, the PI3K gamma selective compound has a delta/gamma selectivity ratio of greater than 1, greater than about 5, greater than about 10, greater than about 50, greater than about 100, greater than about 200, greater than about 400, greater than about 600, greater than about 800, greater than about 1000, greater than about 1500, greater than about 2000, greater than about 5000, greater than about 10,000, or greater than about 20,000. In one embodiment, the PI3K gamma selective compound has a delta/gamma selectivity ratio in the range of from greater than 1 to about 5, from about 5 to about 10, from about 10 to about 50, from about 50 to about 850, or greater than about 850. In one embodiment, the delta/gamma selectivity ratio is determined by dividing the compound's IC_{50} against PI3K delta isoform by the compound's IC_{50} against PI3K gamma isoform.

For example, a compound provided herein with a delta/gamma selectivity ratio of greater than 150 can be combined with a compound that has a gamma/delta selectivity ratio of

1000 at various amounts (e.g., a ratio of 10:1 or 40:1 of a gamma selective compound and a delta selective compound) to provide synergistic effect in cell lines (e.g., diffuse large B-cell lymphoma cell lines such as SU-DHL-4).

In some embodiments, provided herein is a method for using a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, in combination with radiation therapy in inhibiting abnormal cell growth or treating the hyperproliferative disorder in the subject. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein. The administration of a compound provided herein in this combination therapy can be determined as described herein.

Radiation therapy can be administered through one of several methods, or a combination of methods, including without limitation, external-beam therapy, internal radiation therapy, implant radiation, stereotactic radiosurgery, systemic radiation therapy, radiotherapy and permanent or temporary interstitial brachytherapy. The term "brachytherapy," as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. The term is intended without limitation to include exposure to radioactive isotopes (e.g., At-211, I-131, I-125, Y-90, Re-186, Re-188, Sm-153, Bi-212, P-32, and radioactive isotopes of Lu). Suitable radiation sources for use as a cell conditioner as provided herein include both solids and liquids. By way of non-limiting example, the radiation source can be a radionuclide, such as I-125, I-131, Yb-169, Ir-192 as a solid source, I-125 as a solid source, or other radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays. The radioactive material can also be a fluid made from any solution of radionuclide(s), e.g., a solution of I-125 or I-131, or a radioactive fluid can be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, Y-90. Moreover, the radionuclide(s) can be embodied in a gel or radioactive micro spheres.

Without being limited by any theory, a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, can render abnormal cells more sensitive to treatment with radiation for purposes of killing and/or inhibiting the growth of such cells. Accordingly, provided herein is a method for sensitizing abnormal cells in a subject to treatment with radiation which comprises administering to the subject an amount of a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, which amount is effective in sensitizing abnormal cells to treatment with radiation. The amount of the compound used in this method can be determined according to the means for ascertaining effective amounts of such compounds described herein.

In one embodiment, a compound as provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, can be used in combination with an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, and antiproliferative agents, glycolysis inhibitors, or autophagy inhibitors.

Other therapeutic agents, such as MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloproteinase 9) inhibitors, and COX-11 (cyclooxygenase 11) inhibitors, can be used in conjunction with a compound provided herein, or a pharmaceutically acceptable form thereof, or a pharmaceutical composition described herein. Such therapeutic agents include, for example, rapamycin, temsirolimus (CCI-779), everolimus (RAD001), sorafenib, sunitinib, and bevacizumab. Examples of useful COX-II inhibitors include CELEBREX™ (alecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published Oct. 24, 1996), WO 96/27583 (published Mar. 7, 1996), European Patent Application No. 97304971.1 (filed Jul. 8, 1997), European Patent Application No. 99308617.2 (filed Oct. 29, 1999), WO 98/07697 (published Feb. 26, 1998), WO 98/03516 (published Jan. 29, 1998), WO 98/34918 (published Aug. 13, 1998), WO 98/34915 (published Aug. 13, 1998), WO 98/33768 (published Aug. 6, 1998), WO 98/30566 (published Jul. 16, 1998), European Patent Publication 606,046 (published Jul. 13, 1994), European Patent Publication 931, 788 (published Jul. 28, 1999), WO 90/05719 (published May 31, 1990), WO 99/52910 (published Oct. 21, 1999), WO 99/52889 (published Oct. 21, 1999), WO 99/29667 (published Jun. 17, 1999), PCT International Application No. PCT/IB98/01113 (filed Jul. 21, 1998), European Patent Application No. 99302232.1 (filed Mar. 25, 1999), Great Britain Patent Application No. 9912961.1 (filed Jun. 3, 1999), U.S. Provisional Application No. 60/148,464 (filed Aug. 12, 1999), U.S. Pat. No. 5,863,949 (issued Jan. 26, 1999), U.S. Pat. No. 5,861,510 (issued Jan. 19, 1999), and European Patent Publication 780,386 (published Jun. 25, 1997), all of which are incorporated herein in their entireties by reference. In some embodiments, MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. Other embodiments include those that selectively inhibit MMP-2 and/or AMP-9 relative to the other matrix-metalloproteinases (e.g., MAP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13). Some non-limiting examples of MMP inhibitors are AG-3340, RO 32-3555, and RS 13-0830.

Autophagy inhibitors include, but are not limited to, chloroquine, 3-methyladenine, hydroxychloroquine (Plaquenil™), bafilomycin A1, 5-amino-4-imidazole carboxamide riboside (AICAR), okadaic acid, autophagy-suppressive algal toxins which inhibit protein phosphatases of type 2A or type 1, analogues of cAMP, and drugs which elevate cAMP levels such as adenosine, LY204002, N6-mercaptopurine riboside, and vinblastine. In addition, antisense or siRNAs that inhibit expression of proteins including, but not limited to ATG5 (which are implicated in autophagy), can also be used.

In some embodiments, provided herein is a method of and/or a pharmaceutical composition for treating a cardiovascular disease in a subject which comprises an amount of a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, and an amount of one or more therapeutic agents use for the treatment of cardiovascular diseases.

Exemplary agents for use in cardiovascular disease applications are anti-thrombotic agents, e.g., prostacyclin and salicylates, thrombolytic agents, e.g., streptokinase, urokinase, tissue plasminogen activator (TPA) and anisoylated plasminogen-streptokinase activator complex (APSAC), anti-platelets agents, e.g., acetyl-salicylic acid (ASA) and clopidrogel, vasodilating agents, e.g., nitrates, calcium channel blocking drugs, anti-proliferative agents, e.g., colchicine and alkylat-

ing agents, intercalating agents, growth modulating factors such as interleukins, transformation growth factor-beta and congeners of platelet derived growth factor, monoclonal antibodies directed against growth factors, anti-inflammatory agents, both steroidal and non-steroidal, and other agents that can modulate vessel tone, function, arteriosclerosis, and the healing response to vessel or organ injury post intervention. Antibiotics can also be included in combinations or coatings. Moreover, a coating can be used to effect therapeutic delivery focally within the vessel wall. By incorporation of the active agent in a swellable polymer, the active agent will be released upon swelling of the polymer.

In one embodiment, a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, can be formulated or administered in conjunction with liquid or solid tissue barriers also known as lubricants. Examples of tissue barriers include, but are not limited to, polysaccharides, polyglycans, seprafilm, interceed and hyaluronic acid.

Medicaments which can be administered in conjunction with a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, include any suitable drugs usefully delivered by inhalation for example, analgesics, e.g., codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g., diltiazem; antiallergics, e.g. cromoglycate, ketotifen or nedocromil; anti-infectives, e.g., cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines or pentamidine; antihistamines, e.g., methapyrilene; anti-inflammatories, e.g., beclomethasone, flunisolide, budesonide, tipredane, triamcinolone acetonide or fluticasone; antitussives, e.g., noscapine; bronchodilators, e.g., ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol, terbutalin, isoetharine, tulobuterol, orciprenaline or (−)-4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]-amino] methyl]benzenemethanol; diuretics, e.g., amiloride; anticholinergics e.g., ipratropium, atropine or oxitropium; hormones, e.g., cortisone, hydrocortisone or prednisolone; xanthines e.g., aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, e.g., insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments can be used in the form of salts (e.g., as alkali metal or amine salts or as acid addition salts) or as esters (e.g., lower alkyl esters) to optimize the activity and/or stability of the medicament.

Other exemplary therapeutic agents useful for a combination therapy include, but are not limited to, agents as described above, radiation therapy, hormone antagonists, hormones and their releasing factors, thyroid and antithyroid drugs, estrogens and progestins, androgens, adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones, insulin, oral hypoglycemic agents, and the pharmacology of the endocrine pancreas, agents affecting calcification and bone turnover: calcium, phosphate, parathyroid hormone, vitamin D, calcitonin, vitamins such as water-soluble vitamins, vitamin B complex, ascorbic acid, fat-soluble vitamins, vitamins A, K, and E, growth factors, cytokines, chemokines, muscarinic receptor agonists and antagonists; anticholinesterase agents; agents acting at the neuromuscular junction and/or autonomic ganglia; catecholamines, sympathomimetic drugs, and adrenergic receptor agonists or antagonists; and 5-hydroxytryptamine (5-HT, serotonin) receptor agonists and antagonists.

Therapeutic agents can also include agents for pain and inflammation such as histamine and histamine antagonists, bradykinin and bradykinin antagonists, 5-hydroxytryptamine (serotonin), lipid substances that are generated by biotransformation of the products of the selective hydrolysis of membrane phospholipids, eicosanoids, prostaglandins, thromboxanes, leukotrienes, aspirin, nonsteroidal anti-inflammatory agents, analgesic-antipyretic agents, agents that inhibit the synthesis of prostaglandins and thromboxanes, selective inhibitors of the inducible cyclooxygenase, selective inhibitors of the inducible cyclooxygenase-2, autacoids, paracrine hormones, somatostatin, gastrin, cytokines that mediate interactions involved in humoral and cellular immune responses, lipid-derived autacoids, eicosanoids, β-adrenergic agonists, ipratropium, glucocorticoids, methylxanthines, sodium channel blockers, opioid receptor agonists, calcium channel blockers, membrane stabilizers and leukotriene inhibitors.

Additional therapeutic agents contemplated herein include diuretics, vasopressin, agents affecting the renal conservation of water, rennin, angiotensin, agents useful in the treatment of myocardial ischemia, anti-hypertensive agents, angiotensin converting enzyme inhibitors, β-adrenergic receptor antagonists, agents for the treatment of hypercholesterolemia, and agents for the treatment of dyslipidemia.

Other therapeutic agents contemplated herein include drugs used for control of gastric acidity, agents for the treatment of peptic ulcers, agents for the treatment of gastroesophageal reflux disease, prokinetic agents, antiemetics, agents used in irritable bowel syndrome, agents used for diarrhea, agents used for constipation, agents used for inflammatory bowel disease, agents used for biliary disease, agents used for pancreatic disease. Therapeutic agents include, but are not limited to, those used to treat protozoan infections, drugs used to treat Malaria, Amebiasis, Giardiasis, Trichomoniasis, Trypanosomiasis, and/or Leishmaniasis, and/or drugs used in the chemotherapy of helminthiasis. Other therapeutic agents include, but are not limited to, antimicrobial agents, sulfonamides, trimethoprim-sulfamethoxazole quinolones, and agents for urinary tract infections, penicillins, cephalosporins, and other, β-Lactam antibiotics, an agent containing an aminoglycoside, protein synthesis inhibitors, drugs used in the chemotherapy of tuberculosis, mycobacterium avium complex disease, and leprosy, antifungal agents, antiviral agents including nonretroviral agents and antiretroviral agents.

Examples of therapeutic antibodies that can be combined with a compound provided herein include but are not limited to anti-receptor tyrosine kinase antibodies (cetuximab, panitumumab, trastuzumab), anti CD20 antibodies (rituximab, tositumomab), and other antibodies such as alemtuzumab, bevacizumab, and gemtuzumab.

Moreover, therapeutic agents used for immuno-modulation, such as immuno-modulators, immuno-suppressive agents, tolerogens, and immunostimulants are contemplated by the methods herein. In addition, therapeutic agents acting on the blood and the blood-forming organs, hematopoietic agents, growth factors, minerals, and vitamins, anticoagulant, thrombolytic, and anti-platelet drugs are also contemplated by the methods herein.

In exemplary embodiments, for treating renal carcinoma, one can combine a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, with sorafenib and/or avastin. For treating

an endometrial disorder, one can combine a compound provided herein with doxorubincin, taxotere (taxol), and/or cisplatin (carboplatin). For treating ovarian cancer, one can combine a compound provided herein with cisplatin, carboplatin, docetaxel, doxorubincin, topotecan, and/or tamoxifen. For treating breast cancer, one can combine a compound provided herein with paclitaxel or docetaxel, gemcitabine, capecitabine, tamoxifen, letrozole, erlotinib, lapatinib, PD0325901, bevacizumab, trastuzumab, OSI-906, and/or OSI-930. For treating lung cancer, one can combine a compound as provided herein with paclitaxel, docetaxel, gemcitabine, cisplatin, pemetrexed, erlotinib, PD0325901, and/or bevacizumab.

In some embodiments, the disorder to be treated, prevented and/or managed is a hematological cancer, e.g., lymphoma (e.g., T-cell lymphoma; NHL), myeloma (e.g., multiple myeloma), and leukemia (e.g., CLL), and a compound provided herein is used in combination with: HDAC inhibitors such as vorinostat, romidepsin and ACY-1215; mTOR inhibitors such as everolimus; anti-folates such as pralatrexate; nitrogen mustard such as bendamustine; gemcitabine, optionally in further combination with oxaliplatin; rituximab-cyclophosphamide combination; PI3K inhibitors such as GS-1101, XL 499, GDC-0941, and AMG-319; angiogenesis inhibitors such as pomalidomide or BTK inhibitors such as ibrutinib, AVL-292, Dasatinib, LFM-AI3, ONO-WG-307, and GDC-0834. In some embodiments, the disorder to be treated, prevented and/or managed is DLBCL, and a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, is used in combination with HDAC inhibitors provided herein. In one particular embodiment, the HDAC inhibitor is ACY-1215.

In some embodiments, the disorder to be treated, prevented and/or managed is DLBCL, and a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, is used in combination with BTK inhibitors provided herein. In one particular embodiment, the BTK inhibitor is ibrutinib. In one embodiment, the BTK inhibitor is AVL-292.

In some embodiments, the disorder to be treated, prevented and/or managed is DLBCL, and a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, is used in combination with IRAK inhibitors provided herein. In one particular embodiment, the IRAK4 inhibitor is ND-2110 or ND-2158.

In some embodiments, the disorder to be treated, prevented and/or managed is WM, and a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, is used in combination with BTK inhibitors provided herein. In one particular embodiment, the BTK inhibitor is ibrutinib. In one embodiment, the BTK inhibitor is AVL-292.

In some embodiments, the disorder to be treated, prevented and/or managed is WM, and a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, is used in combination with IRAK4 inhibitors provided herein. In one particular embodiment, the IRAK4 inhibitor is ND-2110 or ND-2158.

In some embodiments, the disorder to be treated, prevented and/or managed is T-ALL, the subject/patient has a PTEN deficiency, and a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, is used in combination with doxorubicin and/or vincristine.

In certain embodiments, wherein inflammation (e.g., arthritis, asthma) is treated, prevented and/or managed, a compound provided herein can be combined with, for example: PI3K inhibitors such as GS-1101, XL 499, GDC-0941, and AMG-319; BTK inhibitors such as ibrutinib and AVL-292; JAK inhibitors such as tofacitinib, fostamatinib, and GLPG0636.

In certain embodiments wherein asthma is treated, prevented and/or managed, a compound provided herein can be combined with, for example: beta 2-agonists such as, but not limited to, albuterol (Proventil®, or Ventolin®), salmeterol (Serevent®), formoterol (Foradil®), metaproterenol (Alupent®), pirbuterol (MaxAir®), and terbutaline sulfate; corticosteroids such as, but not limited to, budesonide (e.g., Pulmicort®), flunisolide (e.g., AeroBid Oral Aerosol Inhaler® or Nasalide Nasal Aerosol®), fluticasone (e.g., Flonase® or Flovent®) and triamcinolone (e.g., Azmacort®); mast cell stabilizers such as cromolyn sodium (e.g., Intal® or Nasalcrom®) and nedocromil (e.g., Tilade®); xanthine derivatives such as, but not limited to, theophylline (e.g., Aminophyllin®, Theo-24® or Theolair®); leukotriene receptor antagonists such as, but are not limited to, zafirlukast (Accolate®), montelukast (Singulair®), and zileuton (Zyflo®); and adrenergic agonists such as, but are not limited to, epinephrine (Adrenalin®, Bronitin®, EpiPen® or Primatene Mist®).

In certain embodiments wherein arthritis is treated, prevented and/or managed, a compound provided herein can be combined with, for example: TNF antagonist (e.g., a TNF antibody or fragment, a soluble TNF receptor or fragment, fusion proteins thereof, or a small molecule TNF antagonist); other biologic antirhheumatics (e.g., IL-6 antagonists, IL-1 antagonists, costimulatory modulators); an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, chrloroquine, hydroxychloroquine sulfate, leflunomide, sulfasalzine, penicillamine); a muscle relaxant; a narcotic; a non-steroid anti-inflammatory drug (NSAID); an analgesic; an anesthetic; a sedative; a local anesthetic; a neuromuscular blocker; an antimicrobial (e.g., an aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a fluoroquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial); an antipsoriatic; a corticosteroid; an anabolic steroid; a cytokine or a cytokine antagonist; a calcineurin inhibitor (e.g., cyclosporine, tacrolimus).

In some embodiments, a compound provided herein (e.g., a compound of Formula I (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof) is administered in combination with an agent for the treatment of rheumatoid arthritis. Examples of agents for the treatment of rheumatoid arthritis include, but are not limited to, various NSAIDs, corticosteroids, sulfasalazine, auranofin, methotrexate, azathioprine, penicillamine, cyclosporine, Arava (leflunomide), TNF inhibitors (e.g., Enbrel (etanercept), Remicade (infliximab), Humira (adalimumab), Simponi (golimumab), and Cimzia (certolizumab)), IL-1 inhibitors (e.g., Kineret (anakinra)), T-cell costimulatory modulators

(e.g., Orencia (abatacept)), Anti-CD20 (e.g., Rituxan (rituximab)), and IL-6 inhibitors (e.g., Actemra (tocilizumab)). In one embodiment, the agent is Cimzia (certolizumab). In another embodiment, the agent is Actemra (tocilizumab).

In some embodiments, a compound provided herein (e.g., a compound of Formula I (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof) is administered in combination with an agent for rheumatology. Examples of agents for rheumatology include, but are not limited to, Rayos (prednisone), Stendra (avanafil), Actemra (tocilizumab), Duexis (ibuprofen and famotidine), Actemra (tocilizumab), Krystexxa (pegloticase), Vimovo (naproxen+ esomeprazole), Cimzia (certolizumab pegol), Colcrys (colchicine), Pennsaid (diclofenac sodium topical solution), Simponi (golimumab), Uloric (febuxostat), Orencia (abatacept), Elaprase (idursulfase), Orencia (abatacept), Vioxx (rofecoxib), Enbrel (etanercept), Humira (adalimumab), Remicade (infliximab), Bextra, Kineret, Remicade (infliximab), Supartz, Mobic (meloxicam), Vivelle (estradiol transdermal system), Lodine XL (etodolac), Arava, Salagen, Arthrotec, Etodolac, Ketoprofen, Synvisc, Tolmetin Sodium, Azulfidine EN-tabs Tablets (sulfasalazine delayed release tablets, USP), and Naprelan (naproxen sodium).

In some embodiments, the second agent is selected from belimumab, AGS-009, rontalizumab, vitamin D3, sifalimumab, AMG 811, IFNα Kinoid, CEP33457, epratuzumab, LY2127399, Ocrelizumab, Atacicept, A-623, SBI-087, AMG557, laquinimod, rapamycin, cyclophosphamide, azathioprine, mycophenolate, leflunomide, methotrexate, CNTO 136, tamibarotene, N-acetylcysteine, CDP7657, hydroxychloroquine, rituximab, carfilzomib, bortezomib, ONX 0914, IMO-3100, DV1179, sulfasalazine, and chloroquine. In one embodiment, the second agent is methotrexate, sulfasalazine, chloroquine, or hydroxychloroquine. In one embodiment, the second agent is methotrexate.

In certain embodiments wherein psoriasis is treated, prevented and/or managed, a compound provided herein can be combined with, for example: budesonide, epidermal growth factor, corticosteroids, cyclosporine, sulfasalazine, aminosalicylates, 6-mercaptopurine, azathioprine, metronidazole, lipoxygenase inhibitors, mesalamine, olsalazine, balsalazide, antioxidants, thromboxane inhibitors, IL-1 receptor antagonists, anti-IL-1β monoclonal antibodies, anti-IL-6 monoclonal antibodies, growth factors, elastase inhibitors, pyridinyl-imidazole compounds, antibodies or agonists of TNF, LT, IL-1, IL-2, IL-6, IL-7, IL-8, IL-15, IL-16, IL-18, EMAP-II, GM-CSF, FGF, and PDGF, antibodies of CD2, CD3, CD4, CD8, CD25, CD28, CD30, CD40, CD45, CD69, CD90 or their ligands, methotrexate, cyclosporine, FK506, rapamycin, mycophenolate mofetil, leflunomide, NSAIDs, ibuprofen, corticosteroids, prednisolone, phosphodiesterase inhibitors, adenosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, IRAK, NIK, IKK, p38, MAP kinase inhibitors, IL-1β converting enzyme inhibitors, TNFα converting enzyme inhibitors, T-cell signaling inhibitors, metalloproteinase inhibitors, sulfasalazine, azathioprine, 6-mercaptopurines, angiotensin converting enzyme inhibitors, soluble cytokine receptors, soluble p55 TNF receptor, soluble p75 TNF receptor, sIL-1RI, sIL-1RII, sIL-6R, anti-inflammatory cytokines, IL-4, IL-10, IL-11, IL-13 and TGFβ.

In certain embodiments wherein fibrosis or fibrotic condition of the bone marrow is treated, prevented and/or managed, a compound provided herein can be combined with, for example, a Jak2 inhibitor (including, but not limited to, INCB018424, XL019, TG101348, or TG101209), an immuno-modulator, e.g., an IMID® (including, but not limited to thalidomide, lenalidomide, or panolinomide), hydroxyurea, an androgen, erythropoietic stimulating agents, prednisone, danazol, HDAC inhibitors, or other agents or therapeutic modalities (e.g., stem cell transplants, or radiation).

In certain embodiments wherein fibrosis or fibrotic condition of the heart is treated, prevented and/or managed, a compound provided herein can be combined with, for example, eplerenone, furosemide, pycnogenol, spironolactone, TcNC100692, torasemide (e.g., prolonged release form of torasemide), or combinations thereof.

In certain embodiments wherein fibrosis or fibrotic condition of the kidney is treated, prevented and/or managed, a compound provided herein can be combined with, for example, cyclosporine, cyclosporine A, daclizumab, everolimus, gadofoveset trisodium (ABLAVAR®), imatinib mesylate (GLEEVEC®), matinib mesylate, methotrexate, mycophenolate mofetil, prednisone, sirolimus, spironolactone, STX-100, tamoxifen, TheraCLEC™, or combinations thereof.

In certain embodiments wherein fibrosis or fibrotic condition of the skin is treated, prevented and/or managed, a compound provided herein can be combined with, for example, Bosentan (Tracleer), p144, pentoxifylline; pirfenidone; pravastatin, STI571, Vitamin E, or combinations thereof.

In certain embodiments wherein fibrosis or fibrotic condition of the gastrointestinal system is treated, prevented and/or managed, a compound provided herein can be combined with, for example, ALTU-135, bucelipase alfa (INN), DCI1020, EUR-1008 (ZENPEP™), ibuprofen, Lym-X-Sorb powder, pancrease MT, pancrelipase (e.g., pancrelipase delayed release), pentade canoic acid (PA), repaglinide, TheraCLEC™, triheptadecanoin (THA), ULTRASE MT20, ursodiol, or combinations thereof.

In certain embodiments wherein fibrosis or fibrotic condition of the lung is treated, prevented and/or managed, a compound provided herein can be combined with, for example, 18-FDG, AB0024, ACT-064992 (macitentan), aerosol interferon-gamma, aerosolized human plasma-derived alpha-1 antitrypsin, alpha1-proteinase inhibitor, ambrisentan, amikacin, amiloride, amitriptyline, anti-*pseudomonas* IgY gargle, ARIKACE™ AUREXIS® (tefibazumab), AZAPRED, azathioprine, azithromycin, azithromycin, AZLI, aztreonam lysine, BIBF1120, Bio-25 probiotic, bosentan, Bramitob®, calfactant aerosol, captopril, CC-930, ceftazidime, ceftazidime, cholecalciferol (Vitamin D3), ciprofloxacin (CIPRO®, BAYQ3939), CNTO 888, colistin CF, combined Plasma Exchange (PEX), rituximab, and corticosteroids, cyclophosphamide, dapsone, dasatinib, denufosol tetrasodium (INS37217), dornase alfa (PULMOZYME®), EPI-hNE4, erythromycin, etanercept, FG-3019, fluticasone, FTI, GC1008, GS-9411, hypertonic saline, ibuprofen, iloprost inhalation, imatinib mesylate (GLEEVEC®), inhaled sodium bicarbonate, inhaled sodium pyruvate, interferon gamma-1b, interferon-alpha lozenges, isotonic saline, IWO01, KB001, losartan, lucinactant, mannitol, meropenem, meropenem infusion, miglustat, minocycline, Moli1901, MP-376 (levofloxacin solution for inhalation), mucoid exopolysaccharide *P. aeruginosa* immune globulin IV, mycophenolate mofetil, n-acetylcysteine, N-acetylcysteine (NAC), NaCl 6%, nitric oxide for inhalation, obramycin, octreotide, oligoG CF-5/20, Omalizumab, pioglitazone, piperacillin-tazobactam, pirfenidone, pomalidomide (CC-4047), prednisone, prevastatin, PRM-151, QAX576, rhD-

NAse, SB656933, SB-656933-AAA, sildenafil, tamoxifen, technetium [Tc-99m] sulfur colloid and Indium [In-111] DTPA, tetrathiomolybdate, thalidomide, ticarcillin-clavulanate, tiotropium bromide, tiotropium RESPIMAT® inhaler, tobramycin (GERNEBCIN®), treprostinil, uridine, valganciclovir (VALCYTE®), vardenafil, vitamin D3, xylitol, zileuton, or combinations thereof.

In certain embodiments wherein fibrosis or fibrotic condition of the liver is treated, prevented and/or managed, a compound provided herein can be combined with, for example, adefovir dipivoxil, candesartan, colchicine, combined ATG, mycophenolate mofetil, and tacrolimus, combined cyclosporine microemulsion and tacrolimus, elastometry, everolimus, FG-3019, Fuzheng Huayu, GI262570, glycyrrhizin (monoammonium glycyrrhizinate, glycine, L-cysteine monohydrochloride), interferon gamma-1b, irbesartan, losartan, oltipraz, ORAL IMPACT®, peginterferon alfa-2a, combined peginterferon alfa-2a and ribavirin, peginterferon alfa-2b (SCH 54031), combined peginterferon alpha-2b and ribavirin, praziquantel, prazosin, raltegravir, ribavirin (REBETOL®, SCH 18908), ritonavir-boosted protease inhibitor, pentoxyphilline, tacrolimus, tauroursodeoxycholic acid, tocopherol, ursodiol, warfarin, or combinations thereof.

In certain embodiments wherein cystic fibrosis is treated, prevented and/or managed, a compound provided herein can be combined with, for example, 552-02, 5-methyltetrahydrofolate and vitamin B12, Ad5-CB-CFTR, Adeno-associated virus-CFTR vector, albuterol, alendronate, alpha tocopherol plus ascorbic acid, amiloride HCl, aquADEK™, ataluren (PTC124), AZD1236, AZD9668, azithromycin, bevacizumab, biaxin (clarithromycin), BIIL 283 BS (amelubent), buprofen, calcium carbonate, ceftazidime, cholecalciferol, choline supplementation, CPX, cystic fibrosis transmembrane conductance regulator, DHA-rich supplement, digitoxin, cocosahexaenoic acid (DHA), doxycycline, ECGC, ecombinant human IGF-1, educed glutathione sodium salt, ergocalciferol (vitamin D2), fluorometholone, gadobutrol (GADOVIST®, BAY86-4875), gentamicin, ghrelin, glargine, glutamine, growth hormone, GS-9411, H5.001CBCFTR, human recombinant growth hormone, hydroxychloroquine, hyperbaric oxygen, hypertonic saline, IH636 grape seed proanthocyanidin extract, insulin, interferon gamma-1b, IoGen (molecular iodine), iosartan potassium, isotonic saline, itraconazole, IV gallium nitrate (GANITE®) infusion, ketorolac acetate, lansoprazole, L-arginine, linezolid, lubiprostone, meropenem, miglustat, MP-376 (levofloxacin solution for inhalation), normal saline IV, Nutropin AQ, omega-3 triglycerides, pGM169/GL67A, pGT-1 gene lipid complex, pioglitazone, PTC124, QAU145, salmeterol, SB656933, SB656933, simvastatin, sitagliptin, sodium 4-phenylbutyrate, standardized turmeric root extract, tgAAVCF, TNF blocker, TOBI, tobramycin, tocotrienol, unconjugated Isoflavones 100, vitamin: choline bitartrate(2-hydroxyethyl)trimethylammonium salt 1:1, VX-770, VX-809, Zinc acetate, or combinations thereof.

In some embodiments, a compound provided herein is administered in combination with an agent that inhibits IgE production or activity. In some embodiments, the PI3K inhibitor (e.g., PI3K3 inhibitor) is administered in combination with an inhibitor of mTOR. Agents that inhibit IgE production are known in the art and they include but are not limited to one or more of TEI-9874, 2-(4-(6-cyclohexyloxy-2-naphtyloxy)phenylacetamide)benzoic acid, rapamycin, rapamycin analogs (i.e. rapalogs), TORC1 inhibitors, TORC2 inhibitors, and any other compounds that inhibit mTORC1 and mTORC2. Agents that inhibit IgE activity include, for example, anti-IgE antibodies such as for example Omalizumab and TNX-901.

In certain embodiments wherein scleroderma is treated, prevented and/or managed, a compound provided herein can be combined with, for example: an immunosuppressant (e.g., methotrexate, azathioprine (Imuran®), cyclosporine, mycophenolate mofetil (Cellcept®), and cyclophosphamide (Cytoxan®)); T-cell-directed therapy (e.g., halofuginone, basiliximab, alemtuzumab, abatacept, rapamycin); B-cell directed therapy (e.g., rituximab); autologous hematopoietic stem cell transplantation; a chemokine ligand receptor antagonist (e.g., an agent that targets the CXCL12/CSCR4 axis (e.g., AMD3100)); a DNA methylation inhibitor (e.g., 5-azacytidine); a histone deacetylase inhibitor (e.g., trichostatin A); a statin (e.g., atorvastatin, simvastatin, pravastatin); an endothelin receptor antagonist (e.g., Bosentan®); a phosphodiesterase type V inhibitor (e.g., Sildenafil®); a prostacyclin analog (e.g., trepostinil); an inhibitor of cytokine synthesis and/or signaling (e.g., Imatinib mesylate, Rosiglitazone, rapamycin, antitransforming growth factor β1 (anti-TGFβ1) antibody, mycophenolate mofetil, an anti-IL-6 antibody (e.g., tocilizumab)); corticosteroids; nonsteroidal anti-inflammatory drugs; light therapy; and blood pressure medications (e.g., ACE inhibitors).

In certain embodiments wherein inflammatory myopathies are treated, prevented and/or managed, a compound provided herein can be combined with, for example: topical creams or ointments (e.g., topical corticosteroids, tacrolimus, pimecrolimus); cyclosporine (e.g., topical cyclosporine); an anti-interferon therapy, e.g., AGS-009, Rontalizumab (rhuMAb IFNalpha), Vitamin D3, Sifalimumab (MEDI-545), AMG 811, IFNα Kinoid, or CEP33457. In some embodiments, the other therapy is an IFN-α therapy, e.g., AGS-009, Rontalizumab, Vitamin D3, Sifalimumab (MEDI-545) or IFNα Kinoid; corticosteroids such as prednisone (e.g., oral prednisone); immunosuppressive therapies such as methotrexate (Trexall®, Methotrexate®, Rheumatrex®), azathioprine (Azasan®, Imuran®), intravenous immunoglobulin, tacrolimus (Prograf®), pimecrolimus, cyclophosphamide (Cytoxan®), and cyclosporine (Gengraf®, Neoral®, Sandimmune®); anti-malarial agents such as hydroxychloroquine (Plaquenil®) and chloroquine (Aralen®); total body irradiation; rituximab (Rituxan®); TNF inhibitors (e.g., etanercept (Enbrel®), infliximab (Remicade®)); AGS-009; Rontalizumab (rhuMAb IFNalpha); Vitamin D3; Sifalimumab (MEDI-545); AMG 811; IFNα Kinoid; CEP33457; agents that inhibit IgE production such as TEI-9874, 2-(4-(6-cyclohexyloxy-2-naphtyloxy)phenylacetamide)benzoic acid, rapamycin, rapamycin analogs (i.e. rapalogs), TORC1 inhibitors, TORC2 inhibitors, and any other compounds that inhibit mTORC1 and mTORC2; agents that inhibit IgE activity such as anti-IgE antibodies (e.g., Omalizumab and TNX-90); and additional therapies such as physical therapy, exercise, rest, speech therapy, sun avoidance, heat therapy, and surgery.

In certain embodiments wherein myositis (e.g., dermatomysitis) is treated, prevented and/or managed, a compound provided herein can be combined with, for example: corticosteroids; corticosteroid sparing agents such as, but not limited to, azathioprine and methotrexate; intravenous immunoglobulin; immunosuppressive agents such as, but not limited to, tacrolimus, cyclophosphamide and cyclosporine; rituximab; TNFα inhibitors such as, but not limited to, etanercept and infliximab; growth hormone; growth hormone secretagogues such as, but not limited to, MK-0677, L-162752, L-163022, NN703 ipamorelin, hexarelin, GPA-748 (KP102, GHRP-2), and LY444711 (Eli Lilly); other growth hormone

release stimulators such as, but not limited to, Geref, GHRH (1-44), Somatorelin (GRF 1-44), ThGRF genotropin, L-DOPA, glucagon, and vasopressin; and insulin-like growth factor.

In certain embodiments wherein Sjögren's syndrome is treated, prevented and/or managed, a compound provided herein can be combined with, for example: pilocarpine; cevimeline; nonsteroidal anti-inflammatory drugs; arthritis medications; antifungal agents; cyclosporine; hydroxychloroquine; prednisone; azathioprine; and cyclophamide.

Further therapeutic agents that can be combined with a compound provided herein can be found in Goodman and Gilman's "*The Pharmacological Basis of Therapeutics*" Tenth Edition edited by Hardman, Limbird and Gilman or the Physician's Desk Reference, both of which are incorporated herein by reference in their entirety.

In one embodiment, the compounds described herein can be used in combination with the agents provided herein or other suitable agents, depending on the condition being treated. Hence, in some embodiments, a compound provided herein, or a pharmaceutically acceptable form thereof, will be co-administered with other agents as described above. When used in combination therapy, a compound described herein, or a pharmaceutically acceptable form thereof, can be administered with a second agent simultaneously or separately. This administration in combination can include simultaneous administration of the two agents in the same dosage form, simultaneous administration in separate dosage forms, and separate administration. That is, a compound described herein and any of the agents described above can be formulated together in the same dosage form and administered simultaneously. Alternatively, a compound provided herein and any of the agents described above can be simultaneously administered, wherein both agents are present in separate formulations. In another alternative, a compound provided herein can be administered just followed by any of the agents described above, or vice versa. In the separate administration protocol, a compound provided herein and any of the agents described above can be administered a few minutes apart, or a few hours apart, or a few days apart.

Administration of a compound provided herein, or a pharmaceutically acceptable form thereof, can be effected by any method that enables delivery of the compound to the site of action. An effective amount of a compound provided herein, or a pharmaceutically acceptable form thereof, can be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, including rectal, buccal, intranasal, and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, as an inhalant, or via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer.

When a compound provided herein, or a pharmaceutically acceptable form thereof, is administered in a pharmaceutical composition that comprises one or more agents, and the agent has a shorter half-life than the compound provided herein, unit dose forms of the agent and the compound as provided herein can be adjusted accordingly.

In some embodiments, the compound provided herein and the second agent are administered as separate compositions, e.g., pharmaceutical compositions. In some embodiments, the PI3K modulator and the agent are administered separately, but via the same route (e.g., both orally or both intravenously). In other embodiments, the PI3K modulator and the agent are administered in the same composition, e.g., pharmaceutical composition.

In some embodiments, a compound provided herein (e.g., a compound of Formula I (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof) is administered in combination with an agent for pulmonary or respiratory diseases. Examples of agents for pulmonary or respiratory diseases include, but are not limited to, Dymista (azelastine hydrochloride and fluticasone propionate), Kalydeco (ivacaftor), Qnasl (beclomethasone dipropionate) nasal aerosol, Rayos (prednisone) delayed-release tablets, Surfaxin (lucinactant), Tudorza Pressair (aclidinium bromide inhalation powder), Arcapta (indacaterol maleate inhalation powder), Daliresp (roflumilast), Xalkori (crizotinib), Cayston (aztreonam for inhalation solution), Dulera (mometasone furoate+formoterol fumarate dihydrate), Teflaro (ceftaroline fosamil), Adcirca (tadalafil), Tyvaso (treprostinil), Alvesco (ciclesonide), Patanase (olopatadine hydrochloride), Letairis (ambrisentan), Xyzal (levocetirizine dihydrochloride), Brovana (arformoterol tartrate), Tygacil (tigecycline), Ketek (telithromycin), Spiriva HandiHaler (tiotropium bromide), Aldurazyme (laronidase), Iressa (gefitinib), Xolair (omalizumab), Zemaira (alpha1-proteinase inhibitor), Clarinex, Qvar (beclomethasone dipropionate), Remodulin (treprostinil), Xopenex, Avelox I.V. (moxifloxacin hydrochloride), DuoNeb (albuterol sulfate and ipratropium bromide), Foradil Aerolizer (formoterol fumarate inhalation powder), Invanz, NasalCrom Nasal Spray, Tavist (clemastine fumarate), Tracleer (bosentan), Ventolin HFA (albuterol sulfate inhalation aerosol), Biaxin XL (clarithromycin extended-release tablets), Cefazolin and Dextrose USP, Tri-Nasal Spray (triamcinolone acetonide spray), Accolate, Cafcit Injection, Proventil HFA Inhalation Aerosol, Rhinocort Aqua Nasal Spray, Tequin, Tikosyn Capsules, Allegra-D, Clemastine fumarate syrup, Curosurf, Dynabac, Infasurf, Priftin, Pulmozyme (dornase alfa), Sclerosol Intrapleural Aerosol, Singulair, Synagis, Ceftin (cefuroxime axetil), Cipro (ciprofloxacin HCl), Claritin RediTabs (10 mg loratadine rapidly-disintegrating tablet), Flonase Nasal Spray, Flovent Rotadisk, Metaprotereol Sulfate Inhalation Solution (5%), Nasacort AQ (triamcinolone acetonide) Nasal Spray, Omnicef, Raxar (grepafloxacin), Serevent, Tilade (nedocromil sodium), Tobi, Vanceril 84 mcg Double Strength (beclomethasone dipropionate, 84 mcg) Inhalation Aerosol, Zagam (sparfloxacin) tablets, Zyflo (Zileuton), Accolate, Allegra (fexofenadine hydrochloride), Astelin nasal spray, Atrovent (ipratropium bromide), Augmentin (amoxicillin/clavulanate), Azmacort (triamcinolone acetonide) Inhalation Aerosol, Breathe Right, Claritin Syrup (loratadine), Claritin-D 24 Hour Extended Release Tablets (10 mg loratadine, 240 mg pseudoephedrine sulfate), Covera-HS (verapamil), Nasacort AQ (triamcinolone acetonide) Nasal Spray, OcuHist, Pulmozyme (dornase alfa), RespiGam (Respiratory Syncitial Virus Immune Globulin Intravenous), Tavist (clemastine fumarate), Tripedia (Diptheria and Tetanus Toxoids and Acellular Pertussis Vaccine Absorbed), Vancenase AQ 84 mcg Double Strength, Visipaque (iodixanol), Zosyn (sterile piperacillin sodium/tazobactam sodium), Cedax (ceftibuten), and Zyrtec (cetirizine HCl). In one embodiment, the agent for pulmonary or respiratory diseases is Arcapta, Daliresp, Dulera, Alvesco, Brovana, Spiriva HandiHaler, Xolair, Qvar, Xopenex, DuoNeb, Foradil Aerolizer, Accolate, Singulair, Flovent Rotadisk, Tilade, Vanceril, Zyflo, or Azmacort Inhalation Aerosol. In one embodiment, the agent for pulmonary or respiratory diseases is Spiriva HandiHaler.

In some embodiments, a compound provided herein (e.g., a compound of Formula I (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof) is administered in combination with an agent for immunology or infectious diseases. Examples of agents for immunology or infectious diseases include, but are not limited to, Horizant (gabapentin enacarbil), Qnasl (beclomethasone dipropionate) nasal aerosol, Rayos (prednisone) delayed-release tablets, Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate), Tudorza Pressair (aclidinium bromide inhalation powder), Arcapta (indacaterol maleate inhalation powder), Benlysta (belimumab), Complera (emtricitabine/rilpivirine/tenofovir disoproxil fumarate), Daliresp (roflumilast), Dificid (fidaxomicin), Edurant (rilpivirine), Firazyr (icatibant), Gralise (gabapentin), Incivek (telaprevir), Nulojix (belatacept), Victrelis (boceprevir), Cayston (aztreonam for inhalation solution), Egrifta (tesamorelin for injection), Menveo (meningitis vaccine), Oravig (miconazole), Prevnar 13 (Pneumococcal 13-valent Conjugate Vaccine), Teflaro (ceftaroline fosamil), Zortress (everolimus), Zymaxid (gatifloxacin ophthalmic solution), Bepreve (bepotastine besilate ophthalmic solution), Berinert (C1 Esterase Inhibitor (Human)), Besivance (besifloxacin ophthalmic suspension), Cervarix [Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant], Coartem (artemether/lumefantrine), Hiberix (Haemophilus b Conjugate Vaccine; Tetanus Toxoid Conjugate), Ilaris (canakinumab), Ixiaro (Japanese Encephalitis Vaccine, Inactivated, Adsorbed), Kalbitor (ecallantide), Qutenza (capsaicin), Vibativ (telavancin), Zirgan (ganciclovir ophthalmic gel), Aptivus (tipranavir), Astepro (azelastine hydrochloride nasal spray), Cinryze (C1 Inhibitor (Human)), Intelence (etravirine), Moxatag (amoxicillin), Rotarix (Rotavirus Vaccine, Live, Oral), Tysabri (natalizumab), Viread (tenofovir disoproxil fumarate), Altabax (retapamulin), AzaSite (azithromycin), Doribax (doripenem), Extina (ketoconazole), Isentress (raltegravir), Selzentry (maraviroc), Veramyst (fluticasone furoate), Xyzal (levocetirizine dihydrochloride), Eraxis (anidulafungin), Gardasil (quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine), Noxafil (posaconazole), Prezista (darunavir), Rotateq (rotavirus vaccine, live oral pentavalent), Tyzeka (telbivudine), Veregen (kunecatechins), Aptivus (tipranavir), Baraclude (entecavir), Tygacil (tigecycline), Ketek (telithromycin), Tindamax, tinidazole, Xifaxan (rifaximin), Amevive (alefacept), FluMist (Influenza Virus Vaccine), Fuzeon (enfuvirtide), Lexiva (fosamprenavir calcium), Reyataz (atazanavir sulfate), Alinia (nitazoxanide), Clarinex, Daptacel, Fluzone Preservative-free, Hepsera (adefovir dipivoxil), Pediarix Vaccine, Pegasys (peginterferon alfa-2a), Restasis (cyclosporine ophthalmic emulsion), Sustiva, Vfend (voriconazole), Avelox I.V. (moxifloxacin hydrochloride), Cancidas, Peg-Intron (peginterferon alfa-2b), Rebetol (ribavirin), Spectracef, Twinrix, Valcyte (valganciclovir HCl), Viread (tenofovir disoproxil fumarate), Xigris (drotrecogin alfa [activated]), ABREVA (docosanol), Biaxin XL (clarithromycin extended-release tablets), Cefazolin and Dextrose USP, Children's Motrin Cold, Evoxac, Kaletra Capsules and Oral Solution, Lamisil (terbinafine hydrochloride) Solution (1%), Lotrisone (clotrimazole/betamethasone diproprionate) lotion, Malarone (atovaquone; proguanil hydrochloride) Tablet, Rapamune (sirolimus) Tablets, Rid Mousse, Tri-Nasal Spray (triamcinolone acetonide spray), Trivagizole 3 (clotrimazole) Vaginal Cream, Trizivir (abacavir sulfate; lamivudine; zidovudine AZT) Tablet, Agenerase (amprenavir), Cleocin (clindamycin phosphate), Famvir (famciclovir), Norvir (ritonavir), Panretin Gel, Rapamune (sirolimus) oral solution, Relenza, Synercid I.V., Tamiflu capsule, Vistide (cidofovir), Allegra-D, CellCept, Clemastine fumarate syrup, Cleocin (clindamycin phosphate), Dynabac, REBETRON™ Combination Therapy, Simulect, Timentin, Viroptic, INFANRIX (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed), Acyclovir Capsules, Aldara (imiquimod), Aphthasol, Combivir, Condylox Gel 0.5% (pokofilox), Famvir (famciclovir), Flagyl ER, Flonase Nasal Spray, Fortovase, INFERGEN (interferon alfacon-1), Intron A (interferon alfa-2b, recombinant), Norvir (ritonavir), Rescriptor Tablets (delavirdine mesylate tablets), SPORANOX (itraconazole), Stromectol (ivermectin), Taxol, Trovan, VIRACEPT (nelfinavir mesylate), Zerit (stavudine), Albenza (albendazole), Apthasol (Amlexanox), Carrington patch, Confide, Crixivan (Indinavir sulfate), Gastrocrom Oral Concentrate (cromolyn sodium), Havrix, Lamisil (terbinafine hydrochloride) Tablets, Leukine (sargramostim), Oral Cytovene, RespiGam (Respiratory Syncitial Virus Immune Globulin Intravenous), Videx (didanosine), Viramune (nevirapine), Vistide (cidofovir), Vitrasert Implant, Zithromax (azithromycin), Cedax (ceftibuten), Clarithromycin (Biaxin), Epivir (lamivudine), Intron A (Interferon alfa-2b, recombinant), Invirase (saquinavir), Valtrex (valacyclovir HCl), Western blot confirmatory device, Zerit (stavudine), and Zyrtec (cetirizine HCl).

In some embodiments, the second agent is an HDAC inhibitor, such as, e.g., belinostat, vorinostat, panobinostat, ACY-1215, or romidepsin.

In some embodiments, the second agent is an mTOR inhibitor, such as, e.g., everolimus (RAD 001).

In some embodiments, the second agent is a proteasome inhibitor, such as, e.g., bortezomib or carfilzomib.

In some embodiments, the second agent is a PKC-β inhibitor, such as, e.g., Enzastaurin (LY317615).

In some embodiments, the second agent is a JAK/STAT inhibitor, such as, e.g., INCB16562 or AZD1480.

In some embodiments, the second agent is an anti-folate, such as, e.g., pralatrexate.

In some embodiments, the second agent is a farnesyl transferase inhibitor, such as, e.g., tipifarnib.

In some embodiments, the second agent is an antibody or a biologic agent, such as, e.g., alemtuzumab, rituximab, ofatumumab, or brentuximab vedotin (SGN-035). In one embodiment, the second agent is rituximab. In one embodiment, the second agent is rituximab and the combination therapy is for treating, preventing, and/or managing iNHL, FL, splenic marginal zone, nodal marginal zone, extranodal marginal zone, and/or SLL.

In some embodiments, a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, is used in combination bendamustine and one additional active agent. In one embodiment, the cancer or hematological malignancy is iNHL.

In some embodiments, a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, is used in combination rituximab and one additional active agent. In one embodiment, the cancer or hematological malignancy is iNHL.

In some embodiments, a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate)

thereof, is used in combination bendamustine and rituximab. In one embodiment, the cancer or hematological malignancy is iNHL.

In some embodiments, a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, is used in combination fludarabine, cyclophosphamide, and rituximab. In one embodiment, the cancer or hematological malignancy is CLL.

In some embodiments, a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, is used in combination with an antibody or a biologic agent, such as, e.g., alemtuzumab, rituximab, ofatumumab, or brentuximab vedotin (SGN-035). In one embodiment, the second agent is rituximab. In one embodiment, the second agent is rituximab and the combination therapy is for treating, preventing, and/or managing iNHL, FL, splenic marginal zone, nodal marginal zone, extranodal marginal zone, and/or SLL.

In some embodiments, a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, is used in combination with an antibody-drug conjugate, such as, e.g., inotuzumab ozogamicin, or brentuximab vedotin.

In some embodiments, a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, is used in combination with a cytotoxic agent, such as, e.g., bendamustine, gemcitabine, oxaliplatin, cyclophosphamide, vincristine, vinblastine, anthracycline (e.g., daunorubicin or daunomycin, doxorubicin), actinomycin, dactinomycin, bleomycin, clofarabine, nelarabine, cladribine, asparaginase, methotrexate, or pralatrexate.

In some embodiments, a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, is used in combination with one or more other anticancer agents or chemotherapeutic agents, such as, e.g., fludarabine, ibrutinib, fostamatinib, lenalidomide, thalidomide, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, or R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin or Hydroxydaunomycin, Vincristine or Oncovin, Prednisone).

In some embodiments, a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, is used in combination with an antibody for a cytokine (e.g., an IL-15 antibody, an IL-21 antibody, an IL-4 antibody, an IL-7 antibody, an IL-2 antibody, an IL-9 antibody). In some embodiments, the second agent is a JAK1 inhibitor, a JAK3 inhibitor, a pan-JAK inhibitor, a BTK inhibitor, an SYK inhibitor, or a PI3K delta inhibitor. In some embodiments, the second agent is an antibody for a chemokine.

Without being limited to a particular theory, a targeted combination therapy described herein has reduced side effect and/or enhanced efficacy. For example, in one embodiment, provided herein is a combination therapy for treating CLL with a compound described herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, and a second active agent (e.g., IL-15 antibodies, IL-21 antibodies, IL-4 antibodies, IL-7 antibodies, IL-2 antibodies, IL-9 antibodies, JAK1 inhibitors, JAK3 inhibitors, pan-JAK inhibitors, BTK inhibitors, SYK inhibitors, and/or PI3K delta inhibitors).

Further without being limited by a particular theory, it was found that a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88) does not affect BTK or MEK pathway. Accordingly, in some embodiments, provided herein is a method of treating or managing cancer or hematological malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with a BTK inhibitor. In one embodiment, the BTK inhibitor is ibrutinib. In one embodiment, the BTK inhibitor is AVL-292. In one embodiment, the cancer or hematological malignancy is DLBCL. In another embodiment, the cancer or hematological malignancy is iNHL. In another embodiment, the cancer or hematological malignancy is CLL.

In other embodiments, provided herein is a method of treating or managing cancer or hematological malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with a MEK inhibitor. In one embodiment, the MEK inhibitor is trametinib/GSK1120212 (N-(3-{3-Cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2H)-yl}phenyl)acetamide), selumetinob (6-(4-bromo-2-chloroanilino)-7-fluoro-N-(2-hydroxyethoxy)-3-methylbenzimidazole-5-carboxamide), pimasertib/AS703026/MSC1935369 ((S)—N-(2,3-dihydroxypropyl)-3-((2-fluoro-4-iodophenyl)amino)isonicotinamide), XL-518/GDC-0973 (1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol), refametinib/BAY869766/RDEA119 (N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide), PD-0325901 (N-[(2R)-2,3-Dihydroxypropoxy]-3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]-benzamide), TAK733 ((R)-3-(2,3-Dihydroxypropyl)-6-fluoro-5-(2-fluoro-4-iodophenylamino)-8-methylpyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione), MEK162/ARRY438162 (5-[(4-Bromo-2-fluorophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1H-benzimidazole-6-carboxamide), RO5126766 (3-[[3-Fluoro-2-(methylsulfamoylamino)-4-pyridyl]methyl]-4-methyl-7-pyrimidin-2-yloxychromen-2-one), WX-554, RO4987655/CH4987655 (3,4-difluoro-2-((2-fluoro-4-iodophenyl)amino)-N-(2-hydroxyethoxy)-5-((3-oxo-1,2-oxazinan-2-yl)methyl)benzamide), or AZD8330 (2-((2-fluoro-4-iodophenyl)amino)-N-(2-hydroxyethoxy)-1,5-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide). In one embodiment, the cancer or hematological malignancy is DLBCL. In another embodiment, the cancer or hematological malignancy is ALL. In another embodiment, the cancer or hematological malignancy is CTCL.

In other embodiments, provided herein is a method of treating or managing cancer or hematological malignancy comprising administering to a patient a therapeutically effec-

tive amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with an EZH2 inhibitor. In one embodiment, the EZH2 inhibitor is EPZ-6438, GSK-126, GSK-343, Ell, or 3-deazaneplanocin A (DNNep). In one embodiment, the cancer or hematological malignancy is DLBCL. In another embodiment, the cancer or hematological malignancy is iNHL. In another embodiment, the cancer or hematological malignancy is ALL. In another embodiment, the cancer or hematological malignancy is CTCL.

In other embodiments, provided herein is a method of treating or managing cancer or hematological malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with a bcl-2 inhibitor. In one embodiment, the BCL2 inhibitor is ABT-199 (4-[4-[[2-(4-Chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl]-N-[[3-nitro-4-[[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl] sulfonyl]-2-[(1H-pyrrolo[2,3-b]pyridin-5-yl)oxy] benzamide), ABT-737 (4-[4-[[2-(4-chlorophenyl)phenyl] methyl]piperazin-1-yl]-N-[4-[[(2R)-4-(dimethylamino)-1-phenylsulfanylbutan-2-yl]amino]-3-nitrophenyl] sulfonylbenzamide), ABT-263 ((R)-4-(4-((4'-chloro-4,4-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl) piperazin-1-yl)-N-((4-((4-morpholino-1-(phenylthio)butan-2-yl)amino)-3((trifluoromethyl)sulfonyl)phenyl)sulfonyl) benzamide), GX15-070 (obatoclax mesylate, (2Z)-2-[(5Z)-5-[(3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-4-methoxypyrrol-2-ylidene]indole; methanesulfonic acid))), or G3139 (Oblimersen). In one embodiment, the cancer or hematological malignancy is DLBCL. In another embodiment, the cancer or hematological malignancy is iNHL. In another embodiment, the cancer or hematological malignancy is CLL. In another embodiment, the cancer or hematological malignancy is ALL. In another embodiment, the cancer or hematological malignancy is CTCL.

In other embodiments, provided herein is a method of treating or managing iNHL comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with rituximab. In one embodiment, the patient is an elderly patient. In another embodiment, iNHL is relapsed or refractory.

In other embodiments, provided herein is a method of treating or managing iNHL comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with bendamustine. In one embodiment, iNHL is relapsed or refractory.

In other embodiments, provided herein is a method of treating or managing iNHL comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with rituximab, and in further combination with bendamustine. In one embodiment, iNHL is relapsed or refractory.

In other embodiments, provided herein is a method of treating or managing iNHL comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with lenalidomide. In one embodiment, iNHL is relapsed or refractory.

In other embodiments, provided herein is a method of treating or managing CLL comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with rituximab. In one embodiment, the patient is an elderly patient. In another embodiment, CLL is relapsed or refractory.

In other embodiments, provided herein is a method of treating or managing CLL comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with bendamustine. In one embodiment, CLL is relapsed or refractory.

In other embodiments, provided herein is a method of treating or managing CLL comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with rituximab, and in further combination with bendamustine. In one embodiment, CLL is relapsed or refractory.

In other embodiments, provided herein is a method of treating or managing CLL comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with lenalidomide. In one embodiment, CLL is relapsed or refractory.

In other embodiments, provided herein is a method of treating or managing DLBCL comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with rituximab. In one embodiment, the patient is an elderly patient. In another embodiment, DLBCL is relapsed or refractory.

In other embodiments, provided herein is a method of treating or managing DLBCL comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with bendamustine. In one embodiment, DLBCL is relapsed or refractory.

In other embodiments, provided herein is a method of treating or managing DLBCL comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with rituximab, and in

further combination with bendamustine. In one embodiment, DLBCL is relapsed or refractory.

In other embodiments, provided herein is a method of treating or managing DLBCL comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with R-GDP (rituximab, cyclophosphamide, vincristine and prednisone). In one embodiment, DLBCL is relapsed or refractory. In another embodiment, the treatment is done subsequent to treatment by R-CHOP.

In other embodiments, provided herein is a method of treating or managing DLBCL comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with ibrutinib. In one embodiment, DLBCL is relapsed or refractory.

In other embodiments, provided herein is a method of treating or managing T-cell lymphoma (PTCL or CTCL) comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with rituximab. In one embodiment, T-cell lymphoma is relapsed or refractory.

In other embodiments, provided herein is a method of treating or managing T-cell lymphoma (PTCL or CTCL) comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with bendamustine. In one embodiment, T-cell lymphoma is relapsed or refractory.

In other embodiments, provided herein is a method of treating or managing T-cell lymphoma (PTCL or CTCL) comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with rituximab, and in further combination with bendamustine. In one embodiment, T-cell lymphoma is relapsed or refractory.

In other embodiments, provided herein is a method of treating or managing T-cell lymphoma (PTCL or CTCL) comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with romidepsin. In one embodiment, T-cell lymphoma is relapsed or refractory.

In other embodiments, provided herein is a method of treating or managing mantle cell lymphoma comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with rituximab. In one embodiment, mantle cell lymphoma is relapsed or refractory.

In other embodiments, provided herein is a method of treating or managing mantle cell lymphoma comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with bendamustine. In one embodiment, mantle cell lymphoma is relapsed or refractory.

In other embodiments, provided herein is a method of treating or managing mantle cell lymphoma comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with rituximab, an din further combination with bendamustine. In one embodiment, mantle cell lymphoma is relapsed or refractory.

In other embodiments, provided herein is a method of treating or managing mantle cell lymphoma comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with ibrutinib. In one embodiment, mantle cell lymphoma is relapsed or refractory.

Further, without being limited by a particular theory, it was found that cancer cells exhibit differential sensitivity profiles to doxorubicin and compounds provided herein. Thus, provided herein is a method of treating or managing cancer or hematological malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with a doxorubicin. In one embodiment, the cancer or hematological malignancy is ALL.

In some embodiments, provided herein is a method of treating or managing cancer or hematological malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with a AraC. In one embodiment, the cancer or hematological malignancy is AML.

In specific embodiments, compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88 or a pharmaceutically acceptable form thereof, is used in combination with one or more second agent or second therapy provided herein.

In some embodiments, the second agent is an antibody-drug conjugate, such as, e.g., inotuzumab ozogamicin, or brentuximab vedotin.

In some embodiments, the second agent is a cytotoxic agent, such as, e.g., bendamustine, gemcitabine, oxaliplatin, cyclophosphamide, vincristine, vinblastine, anthracycline (e.g., daunorubicin or daunomycin, doxorubicin), actinomycin, dactinomycin, bleomycin, clofarabine, nelarabine, cladribine, asparaginase, methotrexate, or pralatrexate.

In some embodiments, the second agent is one or more other anti-cancer agents or chemotherapeutic agents, such as, e.g., fludarabine, ibrutinib, fostamatinib, lenalidomide, thalidomide, rituximab, cyclophosphamide, doxorubicin, vincris-

tine, prednisone, or R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin or Hydroxydaunomycin, Vincristine or Oncovin, Prednisone).

In some embodiments, the second agent is an antibody for a cytokine (e.g., an IL-15 antibody, an IL-21 antibody, an IL-4 antibody, an IL-7 antibody, an IL-2 antibody, an IL-9 antibody). In some embodiments, the second agent is a JAK1 inhibitor, a JAK3 inhibitor, a pan-JAK inhibitor, a BTK inhibitor, an SYK inhibitor, or a PI3K delta inhibitor. In some embodiments, the second agent is an antibody for a chemokine.

Without being limited to a particular theory, a targeted combination therapy described herein has reduced side effect and/or enhanced efficacy. For example, in one embodiment, provided herein is a combination therapy for treating CLL with a compound described herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88) and a second active agent (e.g., IL-15 antibodies, IL-21 antibodies, IL-4 antibodies, IL-7 antibodies, IL-2 antibodies, IL-9 antibodies, JAK1 inhibitors, JAK3 inhibitors, pan-JAK inhibitors, BTK inhibitors, SYK inhibitors, and/or PI3K delta inhibitors).

Further without being limited by a particular theory, it was found that a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88) does not affect BTK or MEK pathway. Accordingly, in some embodiments, provided herein is a method of treating or managing cancer or hematological malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with a BTK inhibitor. In one embodiment, the BTK inhibitor is ibrutinib. In one embodiment, the BTK inhibitor is AVL-292. In one embodiment, the cancer or hematological malignancy is DLBCL. In another embodiment, the cancer or hematological malignancy is CLL.

In other embodiments, provided herein is a method of treating or managing cancer or hematological malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with a MEK inhibitor. In one embodiment, the MEK inhibitor is tametinib, selumetinob, AS703026/MSC1935369, XL-518/GDC-0973, BAY869766/RDEA119, GSK1120212 (trametinib), pimasertib, refametinib, PD-0325901, TAK733, MEK162/ARRY438162, RO5126766, WX-554, RO4987655/CH4987655 or AZD8330. In one embodiment, the cancer or hematological malignancy is DLBCL. In another embodiment, the cancer or hematological malignancy is ALL. In another embodiment, the cancer or hematological malignancy is CTCL.

In other embodiments, provided herein is a method of treating or managing cancer or hematological malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with a bcl-2 inhibitor. In one embodiment, the BCL2 inhibitor is ABT-199, ABT-737, ABT-263, GX15-070 (obatoclax mesylate) or G3139 (Genasense). In one embodiment, the cancer or hematological malignancy is DLBCL. In another embodiment, the cancer or hematological malignancy is ALL. In another embodiment, the cancer or hematological malignancy is CTCL.

Further, without being limited by a particular theory, it was found that cancer cells exhibit differential sensitivity profiles to doxorubicin and compounds provided herein. Thus, provided herein is a method of treating or managing cancer or hematological malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with a doxorubicin. In one embodiment, the cancer or hematological malignancy is ALL.

In some embodiments, provided herein is a method of treating or managing cancer or hematological malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein (e.g., compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with a AraC. In one embodiment, the cancer or hematological malignancy is AML.

In specific embodiments, compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88 or a pharmaceutically acceptable form thereof, is used in combination with one or more second agent or second therapy provided herein.

Further provided herein are methods of modulating kinase activity by contacting a kinase with an amount of a compound provided herein sufficient to modulate the activity of the kinase. Modulate can be inhibiting or activating kinase activity. In some embodiments, provided herein are methods of inhibiting kinase activity by contacting a kinase with an amount of a compound provided herein sufficient to inhibit the activity of the kinase. In some embodiments, provided herein are methods of inhibiting kinase activity in a solution by contacting said solution with an amount of a compound provided herein sufficient to inhibit the activity of the kinase in said solution. In some embodiments, provided herein are methods of inhibiting kinase activity in a cell by contacting said cell with an amount of a compound provided herein sufficient to inhibit the activity of the kinase in said cell. In some embodiments, provided herein are methods of inhibiting kinase activity in a tissue by contacting said tissue with an amount of a compound provided herein sufficient to inhibit the activity of the kinase in said tissue. In some embodiments, provided herein are methods of inhibiting kinase activity in an organism by contacting said organism with an amount of a compound provided herein sufficient to inhibit the activity of the kinase in said organism. In some embodiments, provided herein are methods of inhibiting kinase activity in an animal by contacting said animal with an amount of a compound provided herein sufficient to inhibit the activity of the kinase in said animal. In some embodiments, provided herein are methods of inhibiting kinase activity in a mammal by contacting said mammal with an amount of a compound provided herein sufficient to inhibit the activity of the kinase in said mammal. In some embodiments, provided herein are methods of inhibiting kinase activity in a human by contacting said human with an amount of a compound provided herein sufficient to inhibit the activity of the kinase in said human. In some embodiments, the % of kinase activity after contacting a kinase with a compound provided herein is less than 1, 5, 10, 20, 30, 40, 50, 60, 70, 80 90, 95, or 99% of the kinase activity in the absence of said contacting step.

The examples and preparations provided below further illustrate and exemplify the compounds as provided herein and methods of preparing such compounds. It is to be understood that the scope of the present disclosure is not limited in any way by the scope of the following examples and preparations. In the following examples molecules with a single chiral center, unless otherwise noted, exist as a racemic mixture. Those molecules with two or more chiral centers, unless otherwise noted, exist as a racemic mixture of diastereomers. Single enantiomers/diastereomers can be obtained by methods known to those skilled in the art.

Synthesis of Compounds

In some embodiments, compounds of provided herein may be prepared according to methods known in the art. For example, the compounds provided herein can be synthesized according to the schemes below. Scheme 1, shows the synthesis of amine A-30, F-50, X-40, and H50. Scheme 2 shows the synthesis of amide D-20 and formula I.

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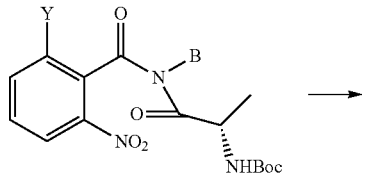
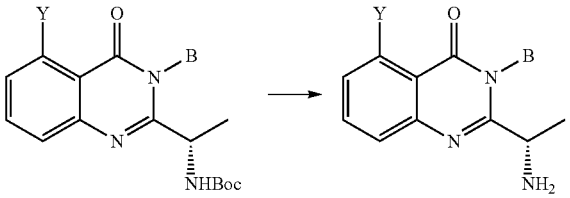


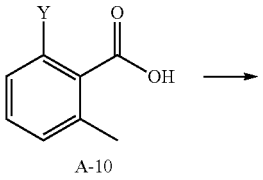
F-30



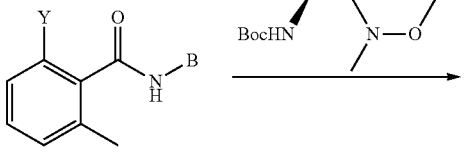
F-40 F-50

Scheme 1

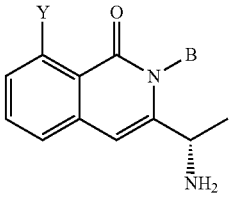
Method A



A-10

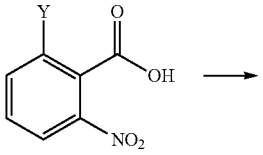


A-20



A-30

Method F



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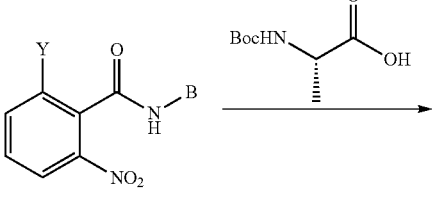
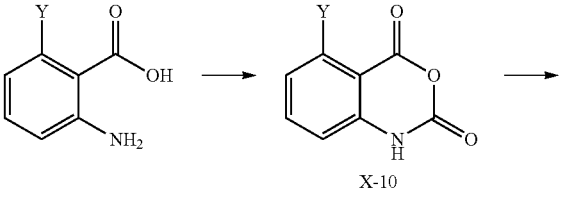
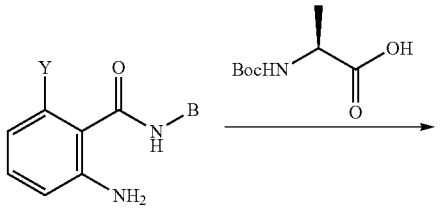


F-20

Method FF



X-10



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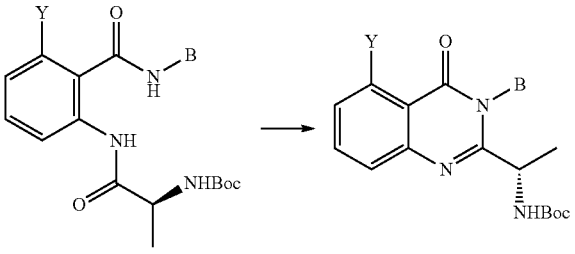
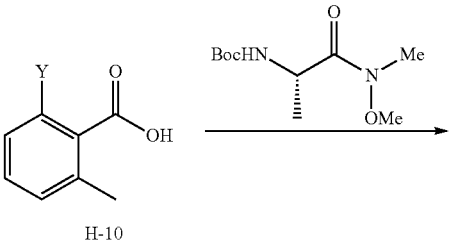


X-30 X-40

Method H



H-10

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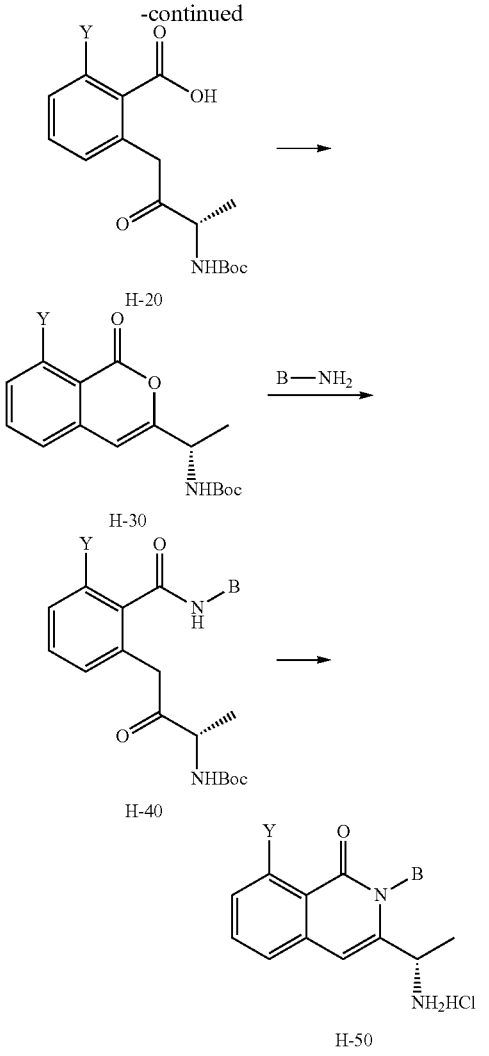
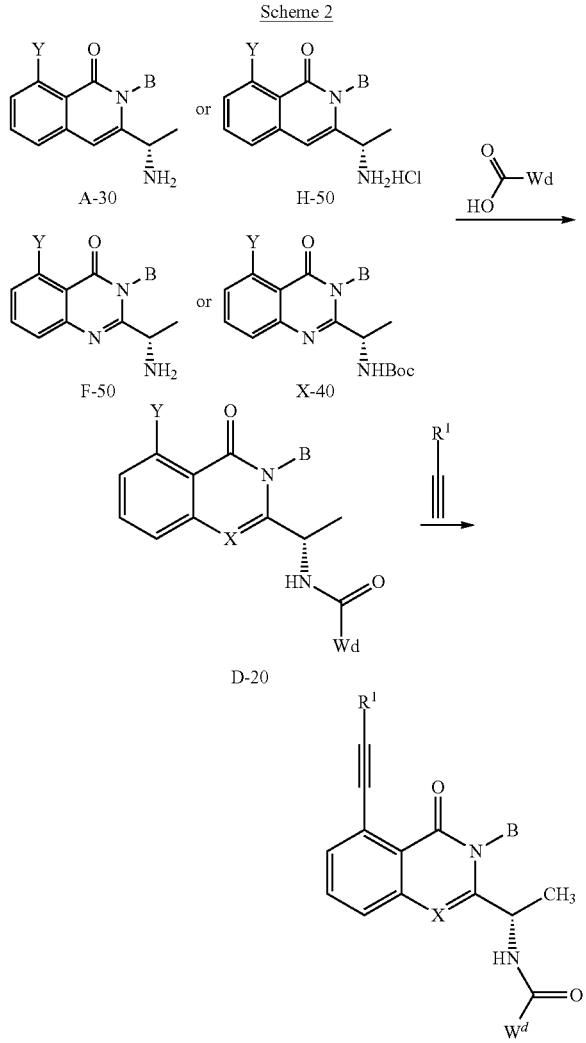


Specifically, in Scheme 1 in method A, isoquinolinone amine compound A-30 is generated in two steps. For example, in the first step, compound A-10 is converted to compound A-20. Compound A-20 is coupled with tert-butyl (1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate to afford compound A-30. In some embodiments, isoquinolinone compounds can be prepared according to method H. For example, compound H-10 is coupled with tert-butyl (1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate to generate compound H-20, which is then converted to H-30. Compound H-30 is reacted with B—NH_2 to form compound H-40, which is then treated with e.g., an acid to afford H-50.

In method F, quinazolinone F-50 is generated. For example, compound F-10 is converted to compound F-20, which couples with 2-((tert-butoxycarbonyl)amino)propanoic acid to form F-30. Compound F-30 is then converted to F-40. Compound F-40 is deprotected to afford compound F-50. Alternatively, quinazolinone X-40 can be prepared starting with 2-amino-6-chlorobenzoic acid to generate compound X-10, which may be converted to compound X-20. Compound X-20 may be coupled with 2-((tert-Butoxycarbonyl)amino)propanoic acid to generate compound X-30, which may be converted to the desired compound X-40.

In Scheme 2, amine compound A30, F50, X-40, or H50 is treated with Wd-C(O)OH to afford amide D20, which is treated with an alkyne to generate a compound of Formula (I).

Scheme 2



EXAMPLES

Chemical Examples

The chemical entities described herein can be synthesized according to one or more illustrative schemes herein and/or techniques well known in the art.

Unless specified to the contrary, the reactions described herein take place at atmospheric pressure, generally within a temperature range from −10° C. to 200° C. Further, except as otherwise specified, reaction times and conditions are intended to be approximate, e.g., taking place at about atmospheric pressure within a temperature range of about −10° C. to about 110° C. over a period that is, for example, about 1 to about 24 hours; reactions left to run overnight in some embodiments can average a period of about 16 hours.

The terms "solvent," "organic solvent," and "inert solvent" each mean a solvent inert under the conditions of the reaction being described in conjunction therewith including, for

example, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), dimethylformamide ("DMF"), chloroform, methylene chloride (or dichloromethane), diethyl ether, methanol, N-methylpyrrolidone ("NMP"), pyridine, and the like. Unless specified to the contrary, the solvents used in the reactions described herein are inert organic solvents. Unless specified to the contrary, for each gram of the limiting reagent, one cc (or mL) of solvent constitutes a volume equivalent.

Isolation and purification of the chemical entities and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure, such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography, or thick-layer chromatography, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures are given by reference to the examples herein below. However, other equivalent separation or isolation procedures can also be used.

When desired, the (R)- and (S)-isomers of the non-limiting exemplary compounds, if present, can be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts or complexes which can be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which can be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. Alternatively, a specific enantiomer can be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation. Further, atropisomers (i.e., stereoisomers from hindered rotation about single bonds) of compounds provided herein can be resolved or isolated by methods known to those skilled in the art. For example, certain B substituents with ortho or meta substituted phenyl may form atropisomers, where they may be separated and isolated.

The compounds described herein can be optionally contacted with a pharmaceutically acceptable acid to form the corresponding acid addition salts. Also, the compounds described herein can be optionally contacted with a pharmaceutically acceptable base to form the corresponding basic addition salts.

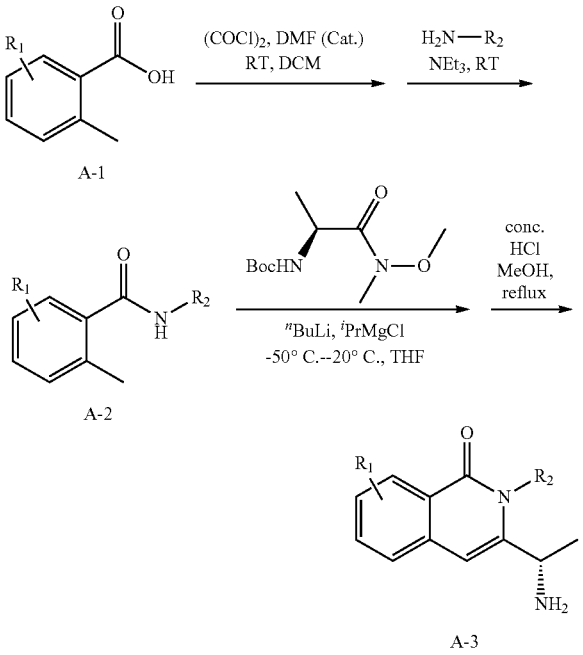
In some embodiments, compounds provided herein can generally be synthesized by an appropriate combination of generally well known synthetic methods. Techniques useful in synthesizing these chemical entities are both readily apparent and accessible to those of skill in the relevant art, based on the instant disclosure. Many of the optionally substituted starting compounds and other reactants are commercially available, e.g., from Aldrich Chemical Company (Milwaukee, Wis.) or can be readily prepared by those skilled in the art using commonly employed synthetic methodology.

The discussion below is offered to illustrate certain of the diverse methods available for use in making the compounds and is not intended to limit the scope of reactions or reaction sequences that can be used in preparing the compounds provided herein.

General Synthetic Methods

The compounds herein being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments, and are not intended to limit these aspects and embodiments.

(i) General Method for the Synthesis of Amine Cores:



Method A

General conditions for the preparation of (S)-3-(1-aminoethyl)-isoquinolin-1(2H-ones

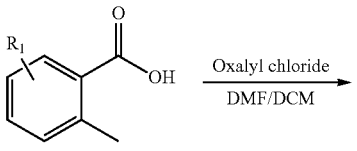
To a stirred mixture of a given o-methylbenzoic acid (A-1) (1 eq, e.g., 1.5 mol) and DMF (catalytic, e.g., 2 mL) in DCM (1.2 M, e.g., 1275 mL) at RT, oxalyl chloride (1.1 eq, e.g., 1.65 mol) is added over 5 min and the resulting mixture is stirred at RT for 2 h. The mixture is then concentrated in vacuo. The residue is dissolved in DCM (150 mL) and the resulting solution (solution A) is used directly in the next step.

To a stirred mixture of aniline (1.05 eq, e.g., 1.58 mol) and triethylamine (2.1 eq, e.g., 3.15 mol) in DCM (1.2 M, e.g., 1350 mL), the above solution A (e.g., 150 mL) is added dropwise while the reaction temperature is maintained between 25° C. to 40° C. by an ice-water bath. The resulting mixture is stirred at RT for 2 h and then water (e.g., 1000 mL) is added. The organic layers are separated and washed with water (2× e.g., 1000 mL), dried over Na_2SO_4 and filtered. The filtrate is concentrated in vacuo. The product is suspended in n-heptanes (e.g., 1000 mL) and stirred at RT for 30 min. The precipitate is collected by filtration, rinsed with heptanes (e.g., 500 mL) and further dried in vacuo to afford the amide (A-2).

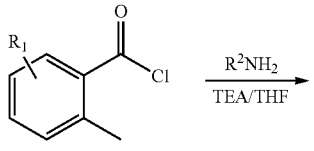
To a stirred mixture of amide (A-2) (1 eq, e.g., 173 mmol) in anhydrous THF (e.g., 250 mL) at −30° C. under an argon atmosphere, a solution of n-butyllithium in hexanes (2.5 eq, 2.5 M, e.g., 432 mol) is added dropwise over 30 min while keeping the inner temperature between −30° C. and −10° C. The resulting mixture is then stirred at −30° C. for 30 min.

To a stirred mixture of (S)-tert-butyl 1-(methoxy(methyl) amino)-1-oxopropan-2-ylcarbamate (1.5 eq, e.g., 260 mmol) in anhydrous THF (e.g., 250 mL) at −30° C. under an argon atmosphere, a solution of isopropylmagnesium chloride in

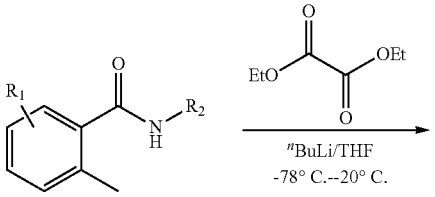
THF (1.65 eq, 1 M, e.g., 286 mmol) is added dropwise over 30 min while keeping inner temperature between −30° C. and −10° C. The resulting mixture is stirred at −30° C. for 30 min. This solution is then slowly added to above reaction mixture while keeping inner temperature between −30° C. and −10° C. The resulting mixture is stirred at −15° C. for 1 h. The reaction mixture is quenched with water (e.g., 50 mL) and then acidified with conc. HCl at −10° C. to 0° C. to adjust the pH to 1-3. The mixture is allowed to warm to RT and concentrated in vacuo. The residue is dissolved in MeOH (e.g., 480 mL), and then conc. HCl (e.g., 240 mL) is added quickly at RT. The resulting mixture is stirred at reflux for 1 h. The reaction mixture is concentrated in vacuo to reduce the volume to about 450 mL. The residue is extracted with a 2:1 mixture of heptane and ethyl acetate (e.g., 2×500 mL). The aqueous layer is basified with concentrated ammonium hydroxide to adjust the pH value to 9-10 while keeping the inner temperature between −10° C. and 0° C. The mixture is then extracted with DCM (e.g., 3×300 mL), washed with brine, dried over $MgSO_4$ and filtered. The filtrate is concentrated in vacuo and the residue is dissolved in MeOH (e.g., 1200 mL) at RT. To this solution, D-(−)-tartaric acid (0.8 eq, e.g., 21 g, 140 mmol) is added in one portion at RT. After stirring at RT for 30 min, a white solid precipitates and the mixture is slurried at RT for 10 h. The solid is collected by filtration and rinsed with MeOH (e.g., 3×50 mL). The collected solid is suspended in water (e.g., 500 mL) and then neutralized with concentrated ammonium hydroxide solution at RT to adjust the pH to 9-10. The mixture is extracted with DCM (e.g., 3×200 mL). The combined organic layers are washed with brine, dried over $MgSO_4$ and filtered. The filtrate is concentrated in vacuo to afford the (S)-3-(1-aminoethyl)-isoquinolin-1(2H)-ones (A-3).



B-1



B-2



B-3

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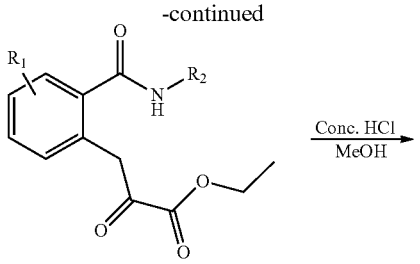

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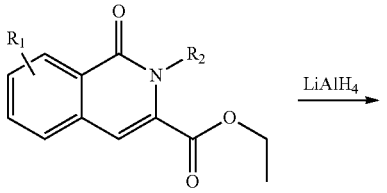
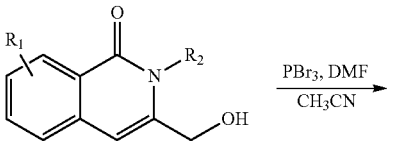


B-5



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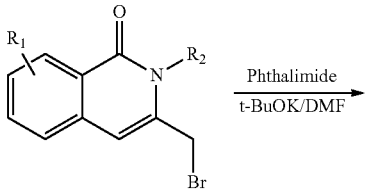
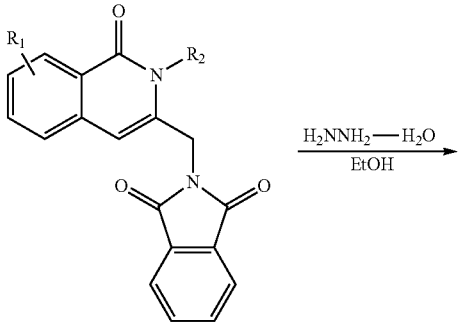
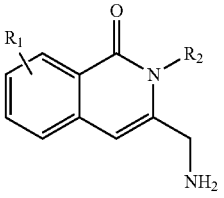


B-7



B-8



B-9

Method B

General conditions for the preparation of 3-(aminomethyl)-isoquinolin-1(2H)-ones

A mixture of benzoic acid (B-1) (1 eq, e.g., 400 mmol), oxalyl chloride (2 eq, e.g., 101 g, 800 mmol) and DMF (catalytic, e.g., 0.2 ml) in DCM (1M, e.g., 400 mL) is stirred

at RT for 2 h. The mixture is concentrated in vacuo to afford the acid chloride (B-2). The product obtained is used directly in the next step without further purification.

A mixture of R_2NH_2 amine (1.05 eq, e.g., 420 mmol) and triethylamine (1.7, e.g., 700 mmol) in DCM (1.4 M, e.g., 300 mL) is stirred at RT for 10 min. To this mixture, acid chloride (B-2) (1 eq, e.g., 400 mmol) is added dropwise, and the resulting mixture is stirred at RT for 30 min. The reaction mixture is poured into water (e.g., 300 mL) and extracted with DCM (e.g., 3×200 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate is concentrated in vacuo to afford the product. The product is suspended in isopropyl ether (e.g., 300 mL), stirred at reflux for 30 min, and then cooled to 0-5° C. The precipitate is collected by filtration and further dried in vacuo to afford the product amide (B-3).

To a stirred solution of amide (B-3) (1.0 eq, e.g., 0.1 mol) in anhydrous THF (0.4 M, e.g., 225 mL) at −78° C. under an argon atmosphere, a solution of n-butyllithium in hexanes (2.5 M, 3 eq, e.g., 120 mL, 0.3 mol) is added dropwise over 1 h period of time while keeping inner temperature between −78° C. to −50° C. The resulting mixture is stirred at −70° C. for 1 h, and then diethyl oxalate (1.2 eq, e.g., 17.5 g, 0.12 mol) is quickly added (with an increase in temperature to −20° C. upon addition). The mixture is stirred at −50° C. for 10 min, and then quenched with water (e.g., 100 mL). The inorganic salt is removed by filtration, and the filtrate is washed with ethyl acetate (e.g., 2×100 mL). The combined organic layers are washed with brine (e.g., 100 mL), dried over $MgSO_4$ and filtered. The filtrate is concentrated in vacuo to afford the product as a semi-solid. The product is slurried in isopropyl ether (e.g., 100 mL) at RT for 10 min. The solid is collected by filtration and further dried in vacuo to afford the product (B-4). The product obtained is used directly in the next step.

Compound (B-4) (1 eq, e.g., 88 mmol) is dissolved at 0.9 M with HCl/MeOH (100 mL, e.g., 10 M), and the resulting mixture is stirred at reflux for 1 h. The reaction mixture is concentrated in vacuo, and the residue is slurried in ethyl acetate (100 mL) at RT for 30 min. The solid is collected by filtration, rinsed with ethyl acetate (3×50 mL), and further dried in vacuo to afford the product (B-5).

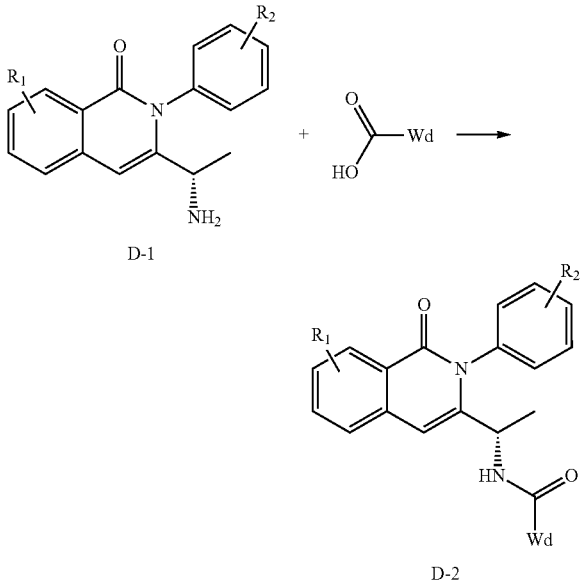
To a stirred suspension of lithium aluminum hydride (3 eq., e.g., 15.6 g, 410 mmol) in anhydrous THF (0.3 M, e.g., 500 mL) at −78° C. under a nitrogen atmosphere, (B-5) (1 eq, e.g., 137 mmol) is slowly added over a 10 min period of time. The resulting mixture is allowed to warm to −30° C. and stirred for 30 min. The mixture is then cooled to −78° C., and quenched carefully with water (e.g., 100 mL). The mixture is allowed to warm to RT, filtered through silica gel (e.g., 20 g), and the filtrate is concentrated in vacuo. The product mixture is poured into H_2O (e.g., 200 mL) and extracted with ethyl acetate (e.g., 3×200 mL). The combined organic layers are washed with brine (e.g., 100 mL), dried over Na_2SO_4 and filtered. The filtrate is concentrated in vacuo. The product is suspended in ethyl acetate (e.g., 30 mL) and stirred for 10 min. The solid is collected by filtration and further dried in vacuo to afford the product (B-6).

Phosphorus tribromide (1.2 eq, e.g., 3.42 g, 12.6 mmol) and DMF (2.0 eq, e.g., 1.6 g, 21.0 mmol) is dissolved in CH_3CN (0.13 M, e.g., 100 mL) and the resulting mixture is stirred at −10° C. for 10 min. To this mixture, alcohol (B-6) (1.0 eq, 10.5 mmol) is added in portions. The resulting mixture is allowed to warm to RT and stirred for an additional 30 min. The reaction mixture is neutralized with saturated aqueous $NaHCO_3$ solution at 0-5° C. and then filtered. The filtrate is extracted with ethyl acetate (e.g., 3×100 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated in vacuo and the residue is purified by flash column chromatography on silica gel (20% ethyl acetate-petroleum ether) to afford the product bromide (B-7).

To a stirred mixture of phthalimide (1.1 eq, e.g., 6.93 mmol) in DMF (e.g., 20 mL) at RT, potassium-tert-butoxide (1.5 eq, e.g., 1.1 g, 9.45 mmol) is added in portions over 10 min and then bromide (B-7) (1.0 eq, e.g., 6.3 mmol) is added. The resulting mixture is stirred at 100° C. for 2 h. The reaction mixture is allowed to cool to RT and then poured into ice-water (e.g., 30 mL). The mixture is extracted with ethyl acetate (e.g., 3×20 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated in vacuo and the residue is purified by flash column chromatography on silica gel (e.g., 16% ethyl acetate-petroleum ether) to afford the product dione (B-8).

Dione (B-8) (1.0 eq, e.g., 1.5 mmol) and hydrazine hydrate (e.g., 8.0 eq, 600 mg, 12 mmol) are dissolved in EtOH (e.g., 20 mL) and the resulting mixture is stirred at reflux for 1 h. The mixture is allowed to cool to RT and then filtered. The filter cake is washed with EtOH (e.g., 10 mL). The combined filtrate is concentrated in vacuo and the residue is purified by flash column chromatography on silica gel (e.g., 2.5% MeOH-DCM) to afford the amine (B-9).

(ii) General Methods for Amide Synthesis:

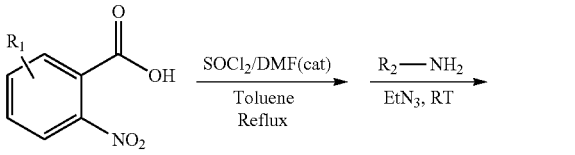


Method D

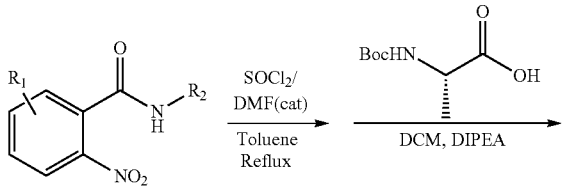
To a mixture of amine (D-1) (1.0 eq, e.g., 0.5 mmol), W_d—COOH carboxylic acid (1.1 eq, e.g., 0.55 mmol), and N,N-diisopropylethylamine (2.0 eq, e.g., 0.17 mL, 1.0 mmol) in anhydrous DMF (e.g., 5 mL), 1-hydroxybenzotriazole hydrate (1.3 eq, e.g., 0.65 mmol) and EDC hydrochloride (1.3 eq, e.g., 0.65 mmol) are added sequentially and the resulting mixture is stirred at RT for 2-16 h. Ice-water or saturated sodium carbonate solution is added to the reaction mixture and then stirred for 10 min. The precipitate is collected by filtration, rinsed with water and dried in vacuo. The solid collected is further purified by flash column chromatography on silica gel (e.g., 0-10% MeOH-DCM) to afford the product amide (D-2).

Method E

A solution of amine (D-1) (1 eq, e.g., 0.25 mmol), W_d—COOH carboxylic acid (1.1 eq), and 1-hydroxybenzotriazole hydrate (1.3 eq) in dimethylformamide (0.1 M) is treated with diisopropylethylamine (2 eq) and then EDC hydrochloride (1.3 eq, e.g., 63 mg). The reaction mixture is stirred at ambient temperature overnight. The reaction mixture is diluted with water (5× solvent) and acetic acid (1.5 eq) is added, then the mixture is stirred in an ice bath for 40 min. The resulting precipitate is collected by filtration, and washed with water (e.g., 3×3 mL). The collected solid is dried in vacuo to afford amide (D-2).



F-1



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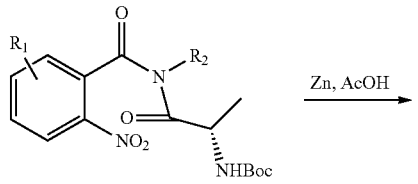

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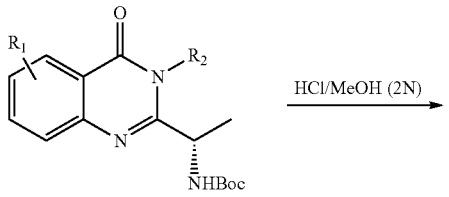

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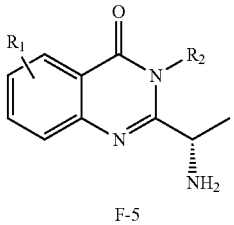


F-5

Method F

To a stirred mixture of nitrobenzoic acid (F-1) (1.0 eq, 1.0 mol) and DMF (e.g., 2.0 mL) in toluene (e.g., 800 mL), thionyl chloride (4.0 eq, e.g., 292 mL, 1.0 mol) is added dropwise (over 15 min) and the resulting mixture is stirred at reflux for 1.5 h. The mixture is allowed to cool to RT and then concentrated in vacuo. The residue is dissolved in DCM (e.g., 100 mL) to form solution A, which is used directly in the next step.

To a stirred mixture of a given amine R_2—NH_2 (1.1 eq, e.g., 102.4 g, 1.1 mol) and triethylamine (2.0 eq, e.g., 280 mL, 2.0 mol) in DCM (1.6 M, e.g., 700 mL), solution A is added dropwise while keeping the reaction temperature below 10° C. The resulting mixture is allowed to warm to RT and then stirred at RT overnight. The reaction mixture is diluted with ice-water (e.g., 1.0 L) and stirred for 15 min. The precipitate is collected by filtration, rinsed with isopropyl ether (e.g., 3×100 mL) and petroleum ether (e.g., 3×100 mL), and then dried in vacuo to afford product amide (F-2).

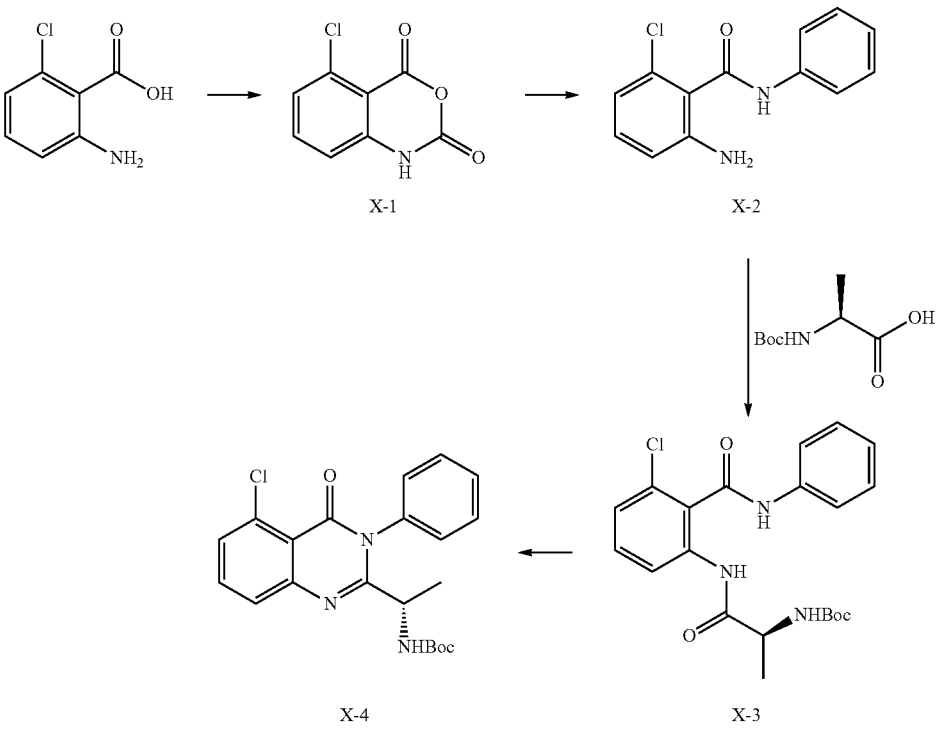
A mixture of nitro-benzamide (F-2) (1.0 eq, e.g., 20.0 mmol) and DMF (cat.) in toluene (0.3 M, e.g., 60 mL) at RT, thionyl chloride (8.2 eq, e.g., 12 mL, 164 mmol) is added dropwise (over 5 min) and the resulting mixture is stirred at reflux for 2 h. The mixture is allowed to cool to RT and then concentrated in vacuo. The residue is dissolved in DCM (e.g., 10 mL) to form solution B, which is used directly in the next step.

To a stirred mixture of N-(tert-butoxycarbonyl)-L-alanine (0.8 eq, e.g., 16.0 mmol) and N,N-diisopropylethylamine (1.5 eq, e.g., 4.0 g, 31.0 mol) in DCM (0.8 M, e.g., 20 mL), solution B is added dropwise while keeping the reaction temperature between 0-10° C. The resulting mixture is stirred at this temperature for 1 h and then stirred at RT overnight. The reaction mixture is quenched with ice-water (e.g., 100 mL). The organic layer is separated and the aqueous layer is extracted with DCM (e.g., 2×80 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated in vacuo and the residue is slurried in isopropyl ether (e.g., 100 mL) for 15 min. The solid is collected by filtration and dried in vacuo to afford product (F-3).

To a suspension of zinc dust (10.0 eq, e.g., 7.2 g, 110 mmol) in glacial acetic acid (2.8 M, e.g., 40 mL) at 15° C., a solution of (F-3) (1.0 eq, e.g., 11.0 mmol) in glacial acetic acid (0.3 M, e.g., 40 mL) is added and the resulting mixture is stirred at RT for 4 h. The mixture is poured into ice-water (e.g., 200 mL) and neutralized with saturated aqueous $NaHCO_3$ solution to adjust the pH to 8. The resulting mixture is extracted with DCM (e.g., 3×150 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated in vacuo and the residue is purified by flash chromatography on silica gel (7% ethyl acetate-petroleum ether) to afford product (F-4).

Compound (F-4) (1.0 eq, e.g., 0.5 mmol) is dissolved in hydrochloric methanol solution (8 eq, e.g., 2N, 20 mL) and the resulting mixture is stirred at RT for 2 h. The mixture is concentrated in vacuo. The residue is diluted with water (30 mL) and then neutralized with saturated aqueous $NaHCO_3$ to adjust the pH to 8 while keeping the temperature below 5° C. The resulting mixture is extracted with DCM (e.g., 3×30 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated in vacuo and the residue is slurried in petroleum ether (e.g., 10 mL). The solid is collected by filtration and dried in vacuo to afford product (F-5).

The quinazolinone (F-5) can be used to synthesize compounds described herein using, for example, Method D to couple the amine to W_d groups.



Method FF

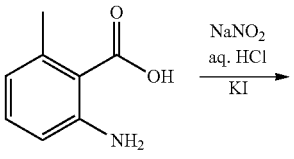
Alternatively, compounds with a quinazolinone core can be prepared according to the procedures in PCT publication no. WO2013082540.

In Method FF, 2-Amino-6-chlorobenzoic acid (63 mmol, 1.0 equiv) is dissolved in acetonitrile (60 mL) in a 250 mL round bottomed-flask, placed under an atmosphere of Ar and heated to 50° C. Pyridine (2.0 equiv) is added followed by dropwise the addition of a solution of triphosgene (0.34 equiv in 30 mL acetonitrile) while maintaining the internal temperature below 60° C. The mixture is then stirred at 50° C. for 2 h after which the solvent is removed under vacuum. The remaining residue is dispersed in 50 mL of water and filtered. The resulting solid is washed with a minimal amount of acetonitrile to remove discoloration and then dried to provide desired anhydride X-1.

Anhydride X-1 (25.5 mmol, 1.0 equiv) is suspended in dioxane (40 mL) under an atmosphere of Ar in a 200 mL round bottomed-flask. Aniline (1.0 equiv) is added dropwise. Heating is started at 40° C. and gradually increased to 100° C. After 4 h, the majority of starting material is consumed after which the reaction is allowed to cool. The solvent is then removed under vacuum to provide an oil which is redissolved in toluene followed by the addition of hexanes until the solvent appears close to partitioning. The mixture is stirred for 14 h after which a solid appeared in the flask. This solid is isolated via vacuum filtration and washed with hexanes to provide the desired amide X-2 in high yield.

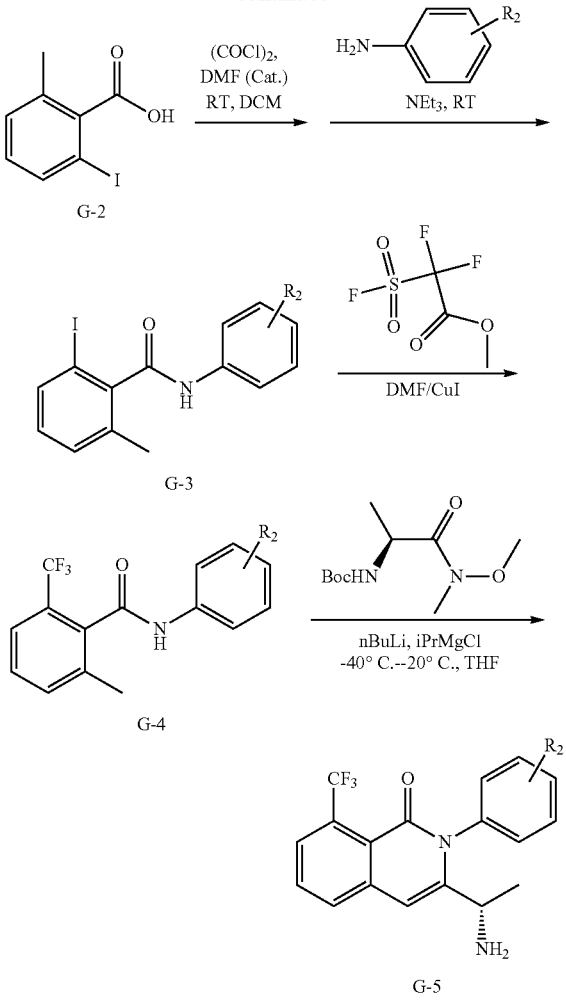
(S)-2-((tert-Butoxycarbonyl)amino)propanoic acid (33.0 mmol, 2.0 equiv) is dissolved in dry tetrahydrofuran (70 mL) under an atmosphere of Ar after which N-methylmorpholine (2.2 equiv) is added dropwise. The mixture is then cooled to −17° C. in an acetone/dry ice bath after which a solution of isobutyl chloroformate (2.0 equiv in 10 mL of dry tetrahydrofuran) is added dropwise to the mixture followed by stirring for 30 min. A solution of amine X-2 (10 equiv in 10 mL of dry tetrahydrofuran) is then added. The dry ice bath is then removed and the mixture is stirred at RT for 90 min. It is then heated to 60° C. for another 2 h after which it is allowed to cool. MTBE (150 mL) and water (150 mL) are then successively added with strong stirring. The phases are separated and the organic phase is washed with water (2×50 mL) and brine (50 mL) and dried over sodium sulfate. The solution is then concentrated under reduced pressure and the crude reside is purified using flash silica gel chromatography (gradient 5-30 ethyl acetate/hexanes) X-3 as the coupled product.

Compound X-3 (4.9 mmol, 1.0 equiv) is then suspended in acetonitrile (100 mL). Triethylamine (48 equiv) is then added with stirring followed by the dropwise addition of chlorotrimethylsilane (15 equiv). The flask is then sealed and heated to 90° C. for 3 d. The reaction is allowed to cool after which the solvent is removed under vacuum. The residue is then dissolved in ethyl acetate (120 mL) and successively washed with saturated sodium carbonate (1×100 mL), water (1×100 mL) and brine (1×100 mL). The organic layer is then dried over anhydrous sodium sulfate and concentrated under reduced pressure to provide cyclized product X-4. The product can either be used directly in subsequent reactions or purified using flash silica gel chromatography.



G-1

-continued



Method G

General conditions for the preparation of (S)-3-(1-aminoethyl)1-8-(trifluoromethyl)isoquinolin-1(2H)-ones

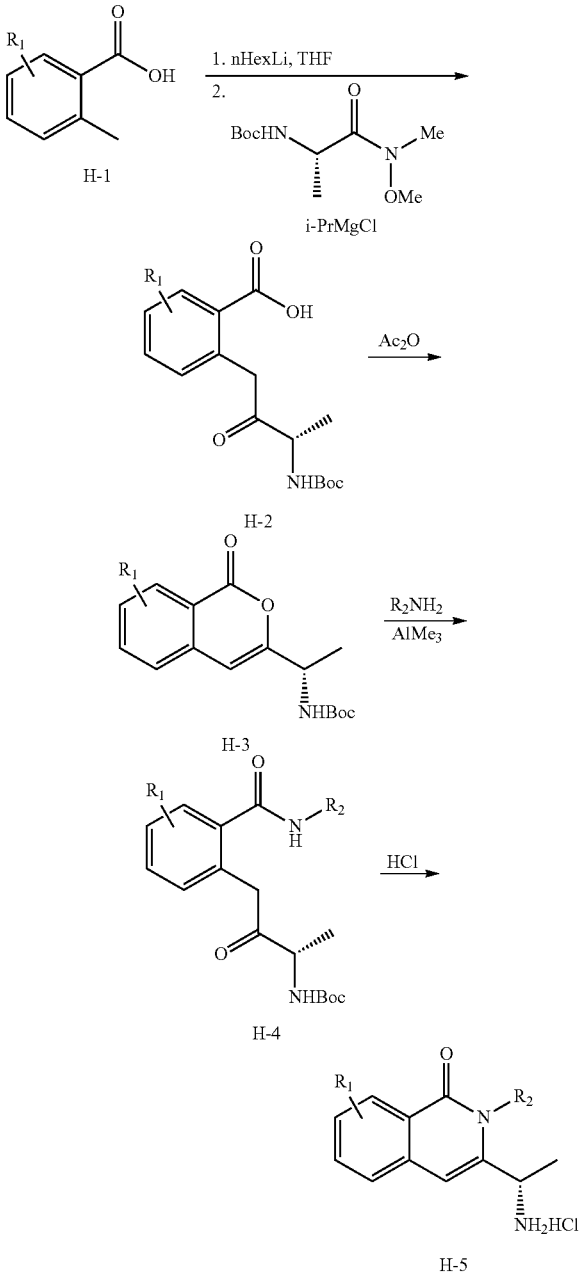
To a suspension of 2-amino-6-methylbenzoic acid (G-1) (20.0 g, 132.0 mmol, 1.0 eq) in H_2O (55 mL) at 0-5° C., conc. HCl (36.5%, 64 mL, 749 mmol, 5.7 eq) is added slowly. After stirring for 15 min, the mixture is added dropwise to a solution of sodium nitrite (12.02 g, 174.0 mmol, 1.32 eq) in H_2O (36 mL) at 0-5° C., and the resulting mixture is stirred for 1 h. The resulting solution is then added to a solution of KI (60.5 g, 364.5 mmol, 2.76 eq) in H_2O (150 mL) at 0-5° C. The reaction mixture is allowed to warm to RT and stirred at RT overnight. The mixture is extracted with ethyl acetate (3×100 mL). The combined organic layers are washed with water (2×100 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate is concentrated in vacuo and the residue is purified by flash column chromatography on silica gel (0-20% ethyl acetate-petro ether) to afford the product, 2-iodo-6-methylbenzoic acid (G-2).

To a stirred mixture of 2-iodo-6-methylbenzoic acid (G-2) (305.3 mmol, 1.0 eq) and DMF (0.3 mL) in DCM (350 mL) at RT, oxalyl chloride (466.4 mmol, 1.5 eq) is added dropwise. The resulting mixture is stirred at RT for 3 h and then concentrated in vacuo. The residue is dissolved in DCM (50 mL) and the resulting solution (solution A) is used directly in the next step.

To a stirred mixture of R_3-substituted aniline (335.7 mmol, 1.1 eq) and triethylamine (915.0 mmol, 3.0 eq) in DCM (350 mL), solution A (150 mL) is added dropwise while the reaction temperature is controlled below 30° C. by an ice-water bath. The reaction mixture is stirred at RT for 1 h and then quenched with water (200 mL). The organic layer is separated, washed with water (2×200 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate is concentrated in vacuo. The product is rinsed with isopropyl ether and dried in vacuo to afford the product amide (G-3).

A mixture of amide (G-3) (18.0 mmol, 1.0 eq), methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (72.9 mmol, 4.0 eq) and CuI (3.63 mmol, 0.2 eq) in DMF (130 mL) is stirred at 70° C. under an argon atmosphere overnight. The mixture is allowed to cool to RT and then concentrated in vacuo to remove the solvent. The resulting residue is partitioned between ethyl acetate (60 mL) and water (60 mL), and the aqueous layer is extracted with ethyl acetate (2×60 mL). The combined organic layers are washed with water (2×60 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate is concentrated in vacuo and the residue is purified by flash column chromatography on silica gel to afford the product, trifluoromethyl amide (G-4).

To a stirred mixture of amide (G-4) (10.1 mmol, 1.0 eq) in anhydrous THF (25 mL) at −40° C. under an argon atmosphere, a solution of n-butyllithium in THF (2.5 M, 25.3 mmol, 2.5 eq) is added dropwise (over 15 min) and the inner temperature is controlled between −30° C. and −20° C. during the addition. The resulting mixture is stirred at −30° C. for an additional 1 h. To a stirred mixture of (S)-tert-butyl 1-(methoxy(methyl)amino)-1-oxopropan-2-ylcarbamate (11.1 mmol, 1.1 eq) in anhydrous THF (20 mL) at −30° C. under an argon atmosphere, a solution of isopropylmagnesium chloride in THF (12.6 mmol, 1.25 eq) is added dropwise (over 15 min) and the inner temperature is controlled below −20° C. during the addition. The resulting mixture is stirred at −15° C. for 1 h. This solution is then slowly added to above reaction mixture at −30° C. (over 10 min), and the resulting mixture is stirred at −30° C. for an additional 30 min. The reaction mixture is quenched with water (50 mL) and then acidified with conc. HCl at −5° C. to adjust the pH to 5. The mixture is allowed to warm to RT and concentrated in vacuo. The residue is dissolved in MeOH (10 mL), and then conc. HCl (10 mL) is added quickly at RT. The resulting mixture is stirred at reflux for 2 h, cooled to RT and then concentrated in vacuo. The residue is suspended in water (15 mL), basified with concentrated ammonium hydroxide to adjust the pH to 9-10 while keeping the inner temperature below 5° C. and then extracted with DCM (3×15 mL). The combined organic layers are washed with brine, dried over $MgSO_4$ and filtered. The filtrate is concentrated in vacuo and the residue is dissolved in MeOH (70 mL). To this solution, D-(−)-tartaric acid (8.1 mmol, 0.8 eq) is added in one portion at RT. After stirring at RT for 30 min, a solid precipitates and the mixture is slurried at RT for 10 h. The precipitate is collected by filtration and rinsed with MeOH (3×4.0 mL). The collected solid is suspended in water (30 mL) and then neutralized with concentrated ammonium hydroxide solution at RT to adjust the pH to 9-10. The mixture is extracted with DCM (3×15 mL). The combined organic layers are washed with brine, dried over anhydrous $MgSO_4$ and filtered. The filtrate is concentrated in vacuo to afford the product, (S)-3-(1-aminoethyl)-8-(trifluoromethyl)isoquinolin-1(2H)-one (G-5).



Method H

General conditions for the preparation of (S)-3-(1-aminoethyl)-isoquinolin-1(2H)-ones

An o-methylbenzoic acid (H-1) (1 eq, e.g., 46.9 mmol) in a flame-dried round bottom flask under nitrogen is dissolved in THF (1 M, e.g., 50 mL). The resulting homogeneous yellow solution is cooled to −25° C. and n-hexyllithium (4.3 eq, e.g., 202 mmol; 2.3 M in hexanes) is slowly added, after which the solution becomes dark red and is stirred at −20° C. for 20 min.

(S)-Tert-butyl 1-(methoxy(methyl)amino)-1-oxopropan-2-ylcarbamate (1.3 eq, e.g., 61.0 mmol) is charged into a second dry round bottom flask under N_2 and suspended in 70 mL of dry THF and cooled to −10° C. Isopropyl magnesium chloride (2 M, 2.7 eq, e.g., 127 mmol) is slowly added resulting in a clear yellow solution. This solution is then slowly cannulated dropwise into the first round bottom flask. After addition is complete, the dark solution is slowly warmed to RT and stirred at RT for 2 h. The reaction mixture is then recooled to −10° C. and quickly cannulated into another flask fitted with ethyl acetate (e.g., 15 mL) and isobutyric acid (e.g., 10 mL) at −10° C. under N_2. During this time the mixture goes from orange and cloudy to clear and homogeneous. After addition, the mixture is stirred for 5 min after which water (e.g., 10 mL) is rapidly added and it is stirred vigorously for 10 min at RT.

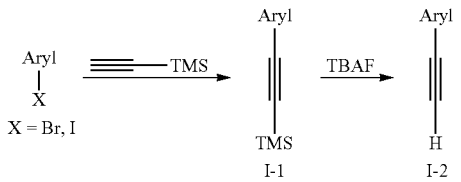
The mixture is then transferred to a separation funnel, and water (e.g., 200 mL) is added to dissolve salts (pH ~9). The water layer is extracted with EtOAc (e.g., 3×400 mL). The aqueous layer is then acidified with HCl (2 M) to pH 3, and then extracted with EtOAc (e.g., 3×500 mL), dried over sodium sulfate and concentrated to provide crude material which is filtered under vacuum through a pad of silica gel using a MeOH/DCM (gradient of 2-10% MeOH) to provide the acid H-2 after concentration.

A 50 mL round bottom flask with a stir bar is filled with benzoic acid H-2 (1 eq., e.g., 14.63 mmol) in acetic anhydride (1.5 M, e.g., 10 mL) and then stirred at 70° C. for 2.5 hours until complete conversion to the product is indicated by LC/MS. The acetic anhydride is evaporated under reduced pressure and the crude residue is purified with combiflash (gradient of EtOAc/hexanes) to give the lactone H-3.

A 50 mL dry round bottom flask with a stir bar is filled with amine R_2NH_2 (5.1 eq, e.g., 1.54 mmol) in 2 mL of DCM (0.8 M) after which trimethylaluminum (5.1 eq, e.g., 1.54 mmol) is added to the solution and stirred for 15 min. A solution of lactone H-3 (1.0 eq, e.g., 0.31 mmol) in DCM (1.5 M, e.g., 2 mL) is then added. The mixture is then stirred at RT for 3 h until LC/MS analysis showed complete formation of the desired product. The reaction mixture is quenched with 10 mL of Rochelle's salt and stirred for 2 h. The mixture is then diluted with DCM, washed with brine, dried with over sodium sulfate and evaporated to give a yellow sticky liquid H-4 which is used directly in next step.

To the amide H-4 (1 eq, e.g., 0.31 mmol) in isopropanol (0.06 M, e.g., 5 mL) was added 3 mL of concentrated HCl (300 eq). The mixture is then heated in an oil bath at 65° C. for 3 h until LC/MS shows no remaining starting material. The flask is then removed from heat and the solvents are evaporated under reduced pressure to provide a yellow solid H-5 which is used directly in subsequent transformations.

(iii) General Methods for Alkyne Synthesis:



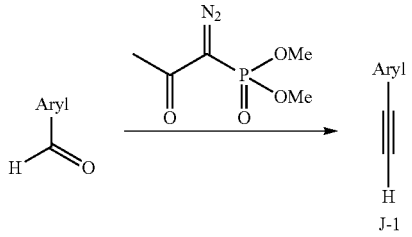
Method I

A sealed vessled is chared with $PdCl_2(MeCN)_2$ and X-Phos (3:1 ratio of X-Phos to $PdCl_2(MeCN)_2$, 5-15 mol % catalyst), cesium carbonate (1.5-3.0 equiv) and propionitrile (0.5 M). The mixture is stirred for 5 min after which the aryl bromide or aryl iodide substrate was added. After another 5 minutes of stirring TMS-acetylene (3.0 equiv) is added and

the flask is sealed and heated at RT for 10 min followed by 1 h of heating at 95° C. The reaction is allowed to cool after which it is concentrated directly onto silica gel and purified using flash silica gel chromatography (gradient of ethyl acetate/hexanes) to provide alkyne I-1.

Alkyne I-1 (1.0 equiv) is then dissolved in tetrahydrofuran (0.13 M) and charged with TBAF (1.1 equiv, 1.0 M in tetrahydrofuran). The resulting mixture is stirred at RT for 6 h after which it is poured into saturated bicarbonate solution and extracted with ethyl acetate. The organic layer is washed with brine and concentrated onto silica gel where it is puffed directly by flash silica gel chromatography (gradient of ethyl acetate/hexanes) to provide aryl alkyne I-2.

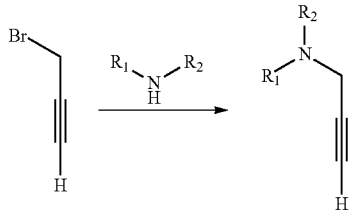
Method J



J-1

Aldehyde (1.0 equiv) was a dissolved in anhydrous methanol (0.2-0.5 mM) and charged with cesium carbonate (1.0 equiv) and cooled to 0-5° C. Dimethyl (1-diazo-2-oxopropyl) phosphonate (1.0 equiv) was added dropwise after which the reaction was allowed to stir for 1-18 h after which the crude mixture was concentrated onto silica gel and purified directly by flash silica gel chromatography to provide the desired alkyne J-1.

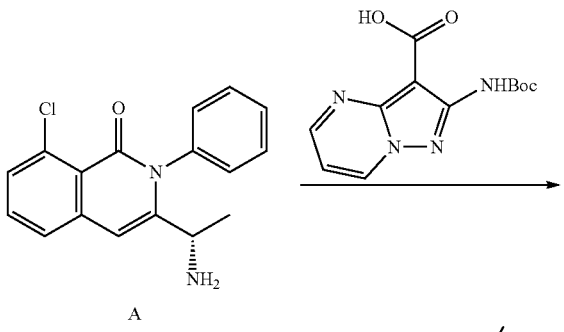
Method K



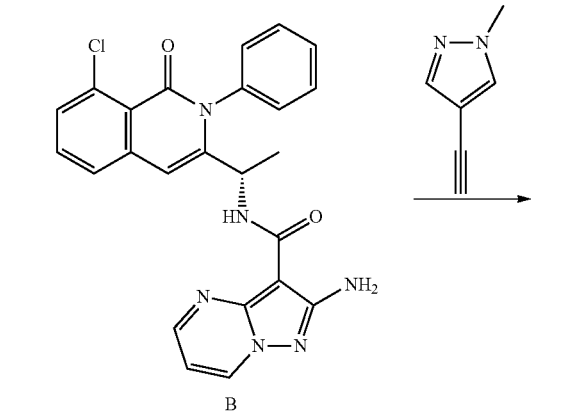
K-1

A secondary amine (1.0 equiv) is dissolved in acetonitrile (0.42 M) and potassium carbonate (1.1 equiv) was added. The white suspension was stirred at 0-5° C. for 5 min after which point propargyl bromide (1.01 equiv) was added dropwise over 3 min. The reaction was then stirred for an additional 15 min at 0-5° C. and then at room temperature for 15 h. The heterogeneous mixture was then filtered. The filtrate was concentrated under reduced pressure, diluted with MTBE and washed with water (2×), brine (1×), dried over sodium sulfate and then filtered through celite. The resulting filtrate was concentrated and purified using flash silica gel chromatography to provide the desired alkyne K-1.

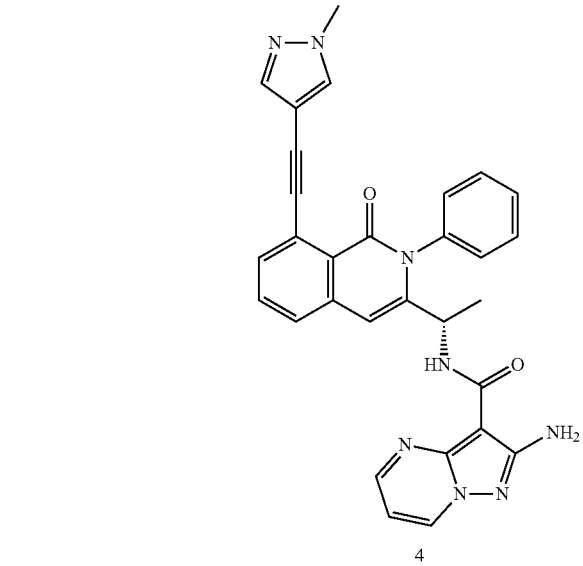
Example 1



A



B



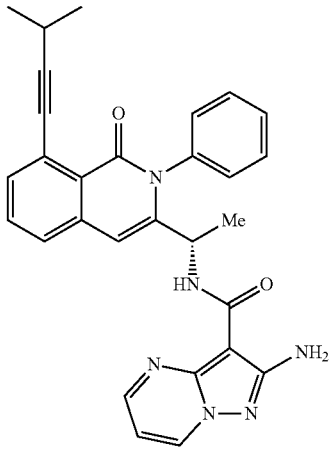
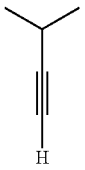
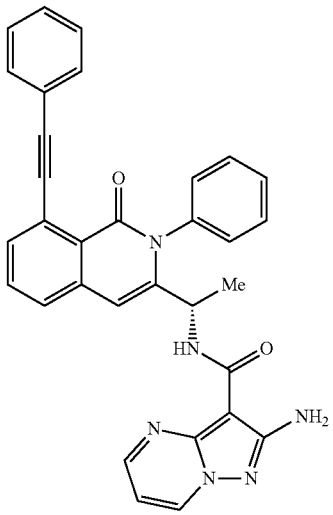
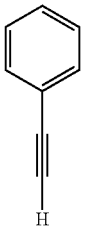
4

Compound 4 was prepared in 3 steps from compound A according to the following procedures: Compound A was prepared according to Method A. It was coupled to 2-((tert-butoxycarbonyl)amino)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid according to the following procedure: Compound A (27.4 mmol, 1.0 equiv), HOBt hydrate (1.2 equiv), 2-((tert-butoxycarbonyl)amino)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (1.05 equiv) and EDC (1.25 equiv) were added to a 200 mL round bottomed flask with a stir bar. N,N-Dimethylformamide (50 mL) was added and the suspen-

sion was stirred at RT for 2 min. Hunig's base (4.0 equiv) was added and after which the suspension became homogeneous and was stirred for 22 h resulting in the formation of a solid cake in the reaction flask. The solid mixture was added to water (600 mL) and stirred for 3 h. The resulting cream colored solid was filtered and washed with water (2×100 mL) and dried. The solid was then dissolved in methylene chloride (40 mL) after which trifluoroacetic acid (10 equiv, 20 mL) was added and the reaction was stirred for 30 min at RT after which there is no more starting material by LC/MS analysis. The solution was then concentrated and coevaporated with a mixture of methylene chloride/ethanol (1:1 v/v) and then dried under high vacuum overnight. The resulting solid was triturated with 60 mL of ethanol for 1 h and then collected via vacuum filtration. The beige solid was then neutralized with sodium carbonate solution (100 mL) and then transferred to a separatory funnel with methylene chloride (350 mL). The water layer was extracted with an additional 100 mL of methylene chloride. The combined organic layers were dried over sodium sulfate, filtered and concentrated under vacuum to provide a pale yellow solid that was purified using flash silica gel chromatography (Combiflash, 24 g column, gradient of 0-5% methanol/methylene chloride) to provide amide B. ESI-MS m/z: 459.4 [M+H]+.

Amide B was placed in a sealed tube (0.67 mmol, 1.0 equiv) followed by dichlorobis(acetonitrile)palladium (15 mol %), X-Phos (45 mol %), and cesium carbonate (3.0 equiv) Propionitrile (5 mL) was added and the mixture was bubbled with Ar for 1 min. 4-Ethynyl-1-methyl-1H-pyrazole (1.24 equiv) was added and the resulting orange mixture was sealed and stirred in an oil bath at 85° C. for 1.5 h. The resulting brownish-black mixture was allowed to cool at which point there was no more SM by LC/MS analysis. The mixture was then filtered through a short plug of cotton using acetonitrile and methylene chloride. The combined filtrates were concentrated onto silica gel and purified using flash silica gel chromatography (Combiflash, 4 g column, gradient of 0-5% methylene chloride/methanol). The resulting material was further purified by reverse phase HPLC (15-90% acetonitrile with 0.1% formic acid/water with 0.1% formic water) to provide desired compound 4. ESI-MS m/z: 529.5 [M+H]+.

The following compounds were prepared in analogous fashion. The alkynes were either commercially available or prepared using Method I, J, or K as described herein.

Compound no.	Structure	Alkyne	ESI-MS m/z
Compound 2			491.1 $[M + H]^+$
Compound 5			525.5 $[M + H]^+$

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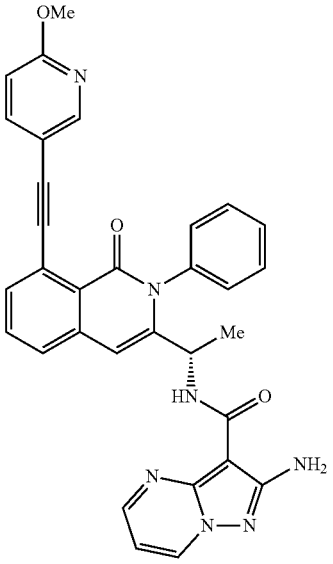
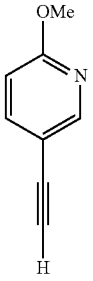
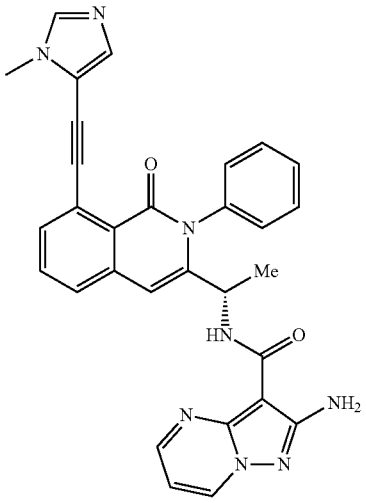
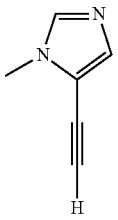
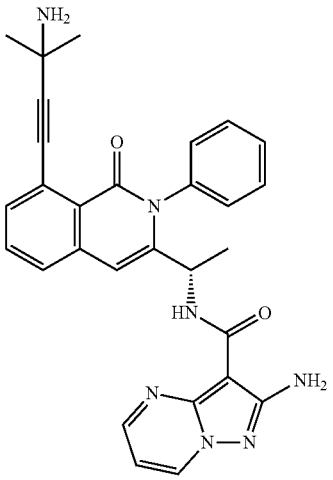
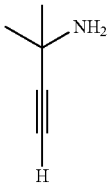
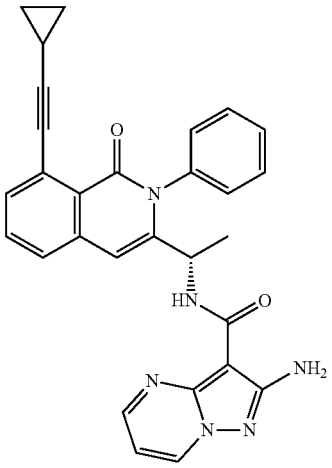
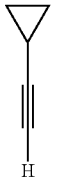
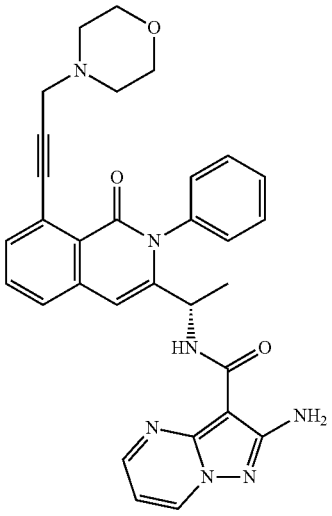
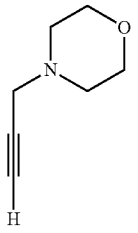
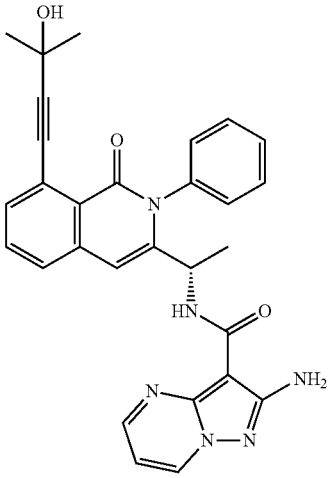
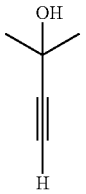
Compound no.	Structure	Alkyne	ESI-MS m/z
Compound 6			556.3 $[M + H]^+$
Compound 7			529.5 $[M + H]^+$
Compound 8			506.1 $[M + H]^+$

-continued

Compound no.	Structure	Alkyne	ESI-MS m/z
Compound 9			489.4 $[M + H]^+$
Compound 10		 Synthesized according to Method K	548.6 $[M + H]^+$
Compound 11			507.1 $[M + H]^+$

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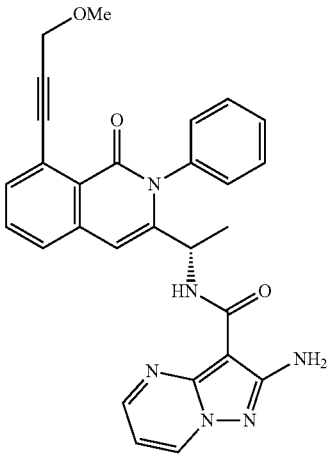
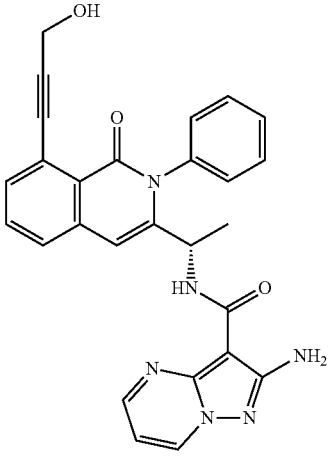
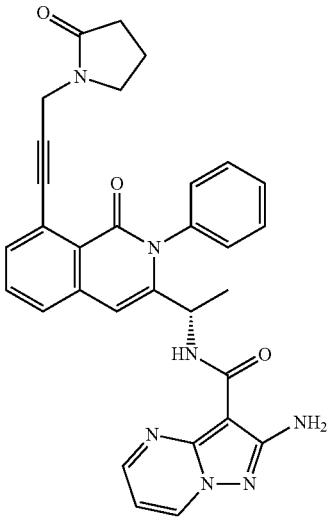
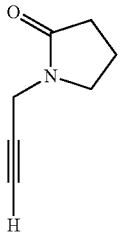
Compound no.	Structure	Alkyne	ESI-MS m/z
Compound 12			493.1 $[M + H]^+$
Compound 13			479.1 $[M + H]^+$
Compound 14			546.5 $[M + H]^+$

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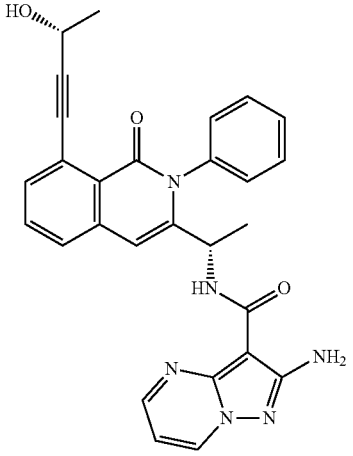
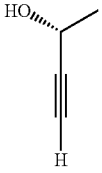
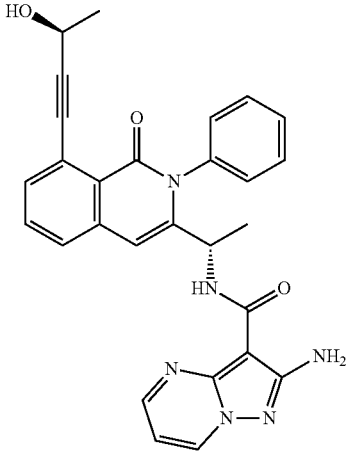
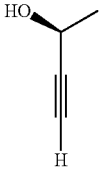
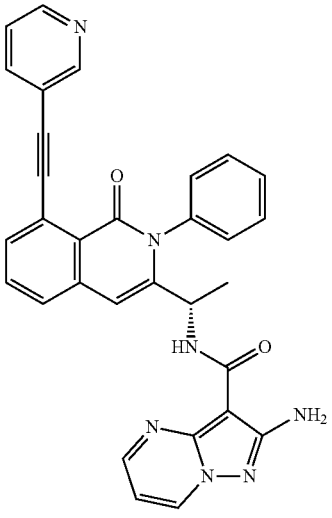
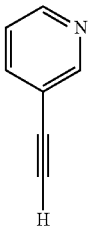
Compound no.	Structure	Alkyne	ESI-MS m/z
Compound 15			493.4 $[M + H]^+$
Compound 16			493.4 $[M + H]^+$
Compound 17			526.5 $[M + H]^+$

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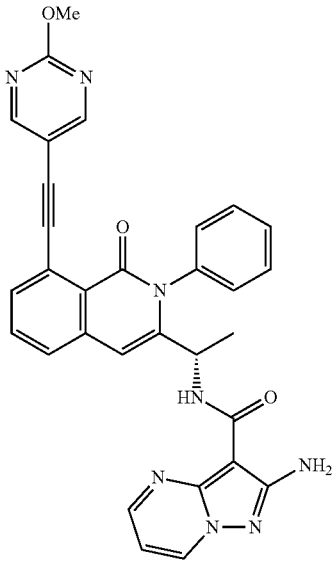
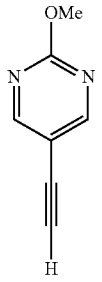
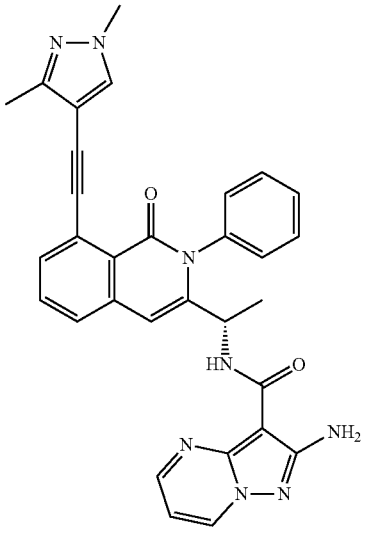
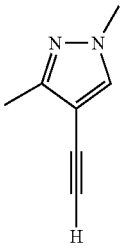
Compound no.	Structure	Alkyne	ESI-MS m/z
Compound 18		 Synthesized according to Method I	557.1 $[M + H]^+$
Compound 19		 Synthesized according to Method I	543.2

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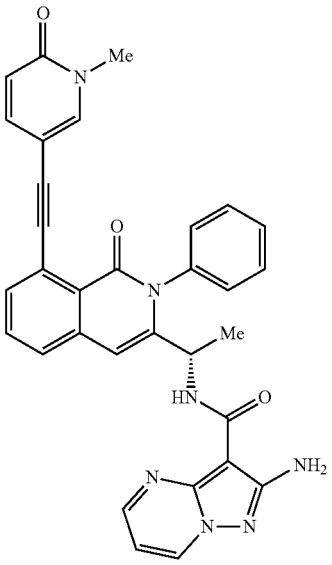
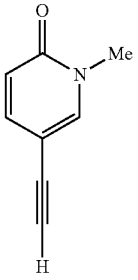
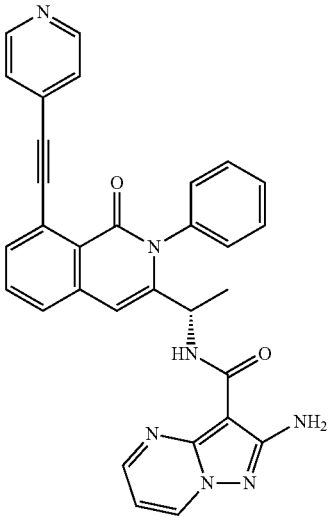
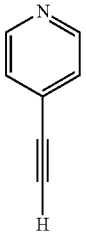
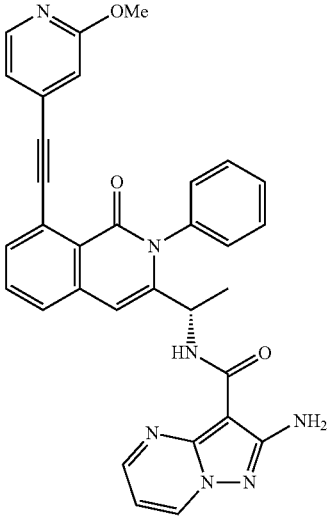
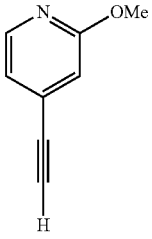
Compound no.	Structure	Alkyne	ESI-MS m/z
Compound 20		 Synthesized according to Method I	556.2 $[M + H]^+$
Compound 26			526.3 $[M + H]^+$
Compound 28		 Synthesized according to Method J	556.3 $[M + H]^+$

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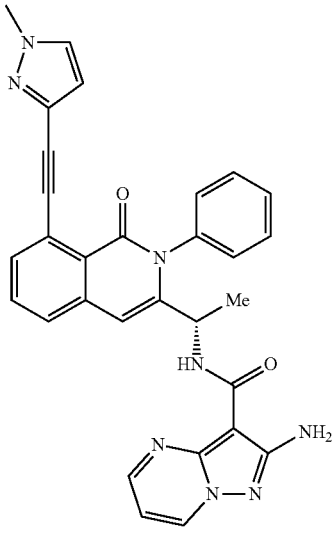
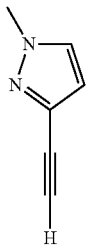
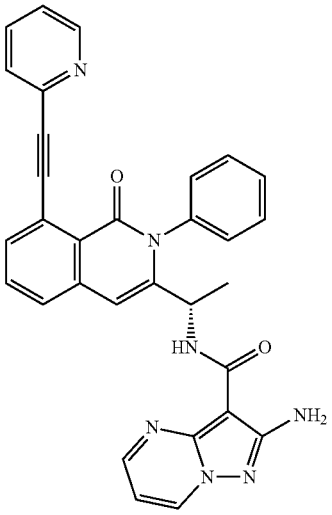
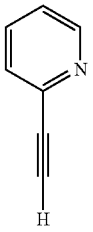
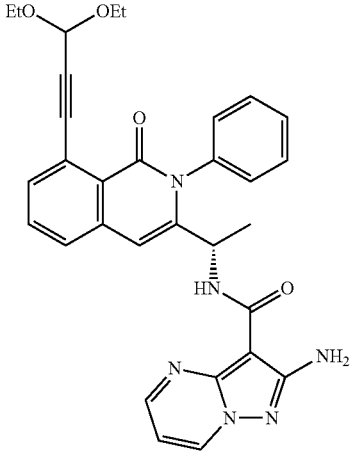
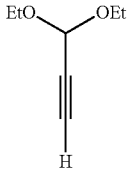
Compound no.	Structure	Alkyne	ESI-MS m/z
Compound 30		 Synthesized according to Method J	529.4 $[M + H]^+$
Compound 32			526.4 $[M + H]^+$
Compound 34			505.3 $[M + H(- OEt)]^+$

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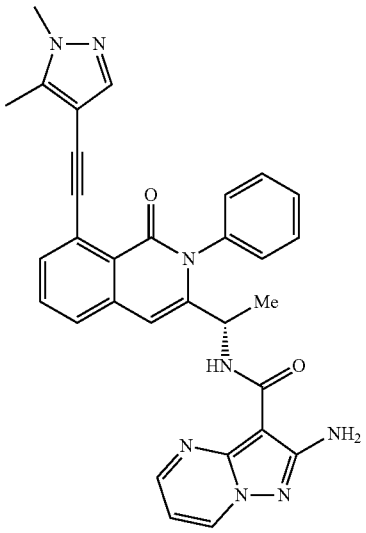
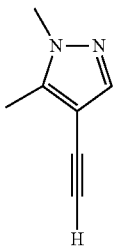
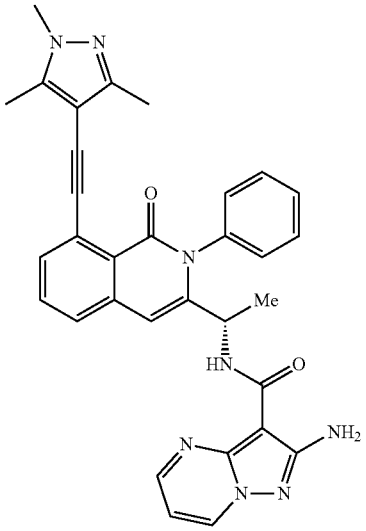
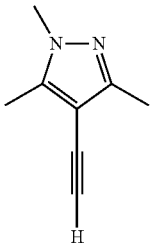
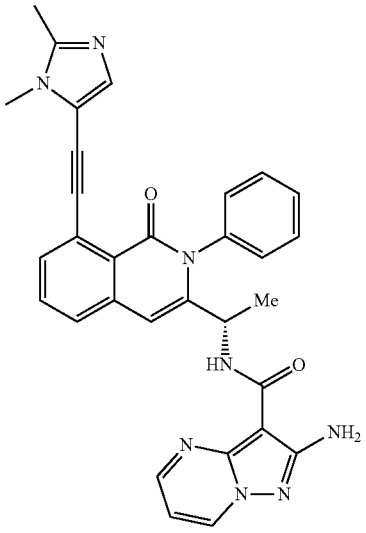
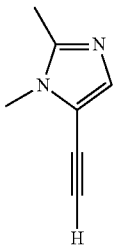
Compound no.	Structure	Alkyne	ESI-MS m/z
Compound 35		 Synthesized according to Method J	543.4 $[M + H]^+$
Compound 37		 Synthesized according to Method J	557.4 $[M + H]^+$
Compound 38		 Synthesized according to Method J	543.4 $[M + H]^+$

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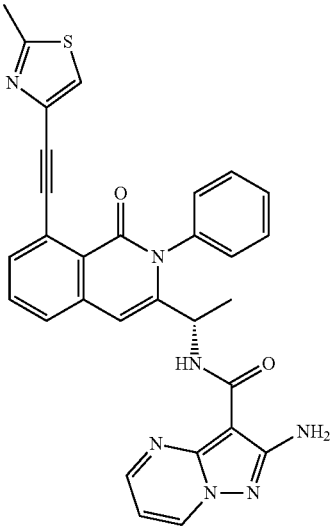
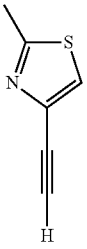
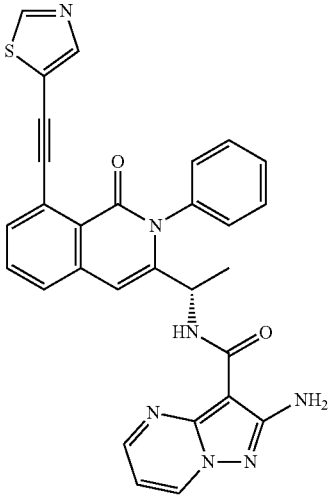
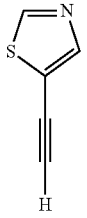
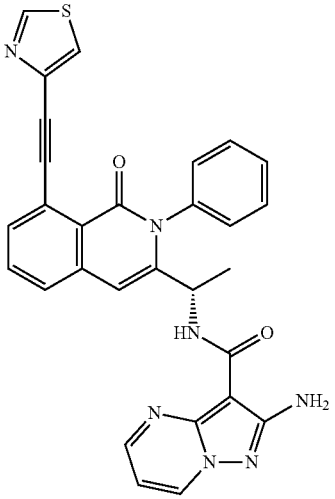
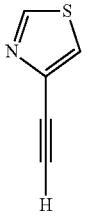
Compound no.	Structure	Alkyne	ESI-MS m/z
Compound 40		 Synthesized according to Method J	546.6 $[M + H]^+$
Compound 41		 Synthesized according to Method J	532.6 $[M + H]^+$
Compound 54		 Synthesized according to Method J	532.6 $[M + H]^+$

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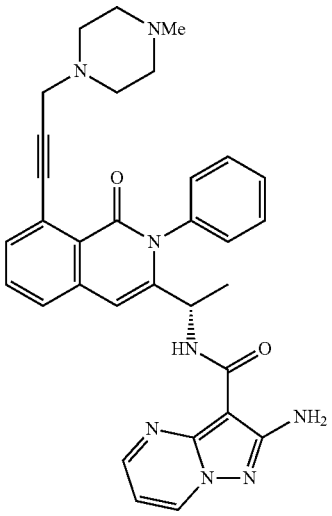
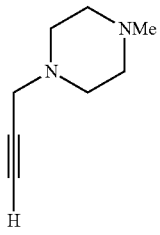
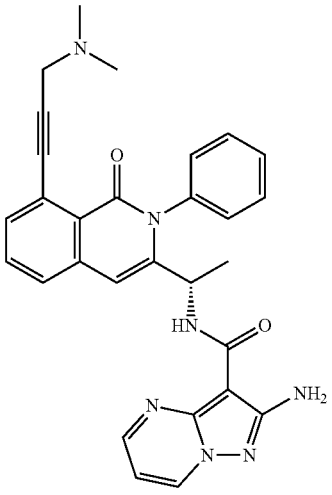
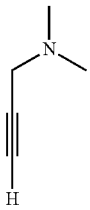
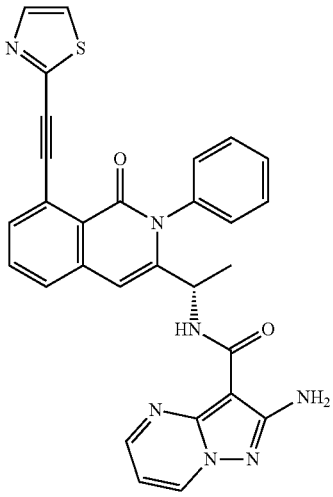
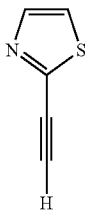
Compound no.	Structure	Alkyne	ESI-MS m/z
Compound 56		 Synthesized according to Method K	561.7 $[M + H]^+$
Compound 57			506.6 $[M + H]^+$
Compound 59		 Synthesized according to Method J	532.5 $[M + H]^+$

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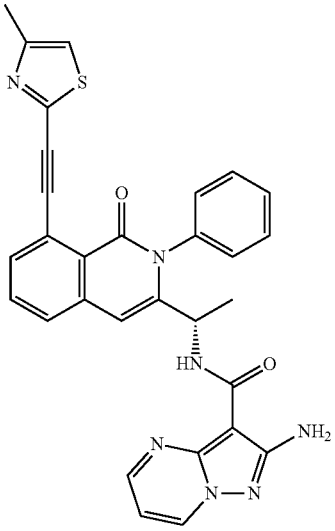
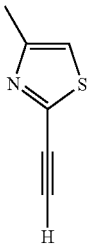
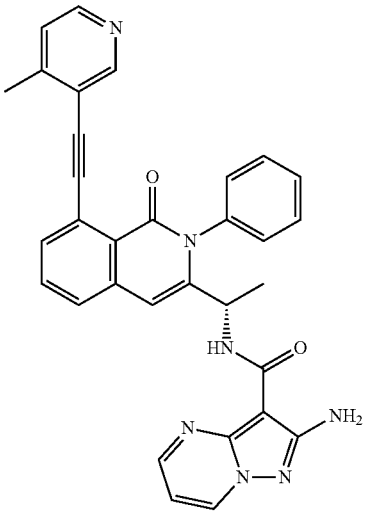
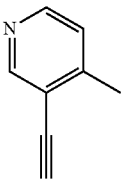
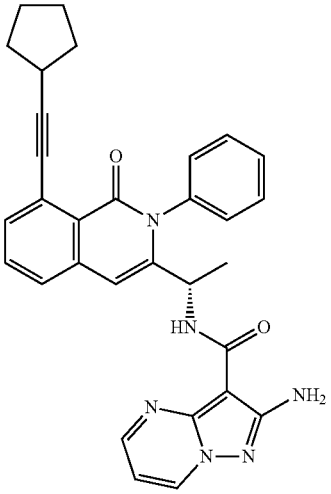
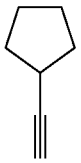
Compound no.	Structure	Alkyne	ESI-MS m/z
Compound 60		 Synthesized according to Method J	545.6 $[M + H]^+$
Compound 61		 Synthesized according to Method J	540.3 $[M + H]^+$
Compound 64			517.6 $[M + H]^+$

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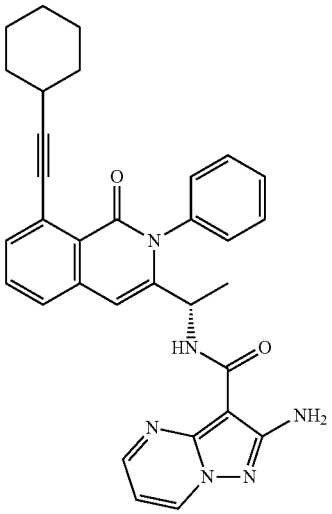
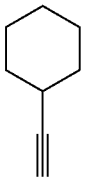
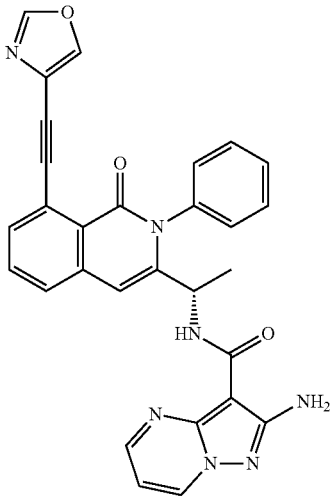
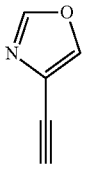
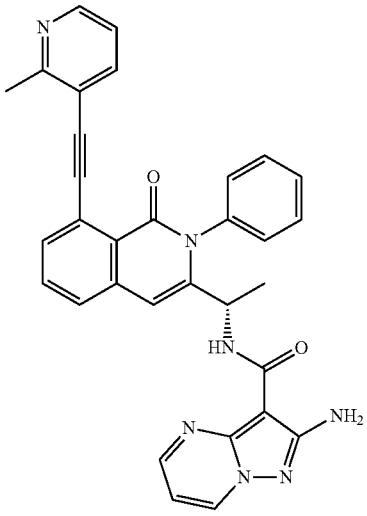
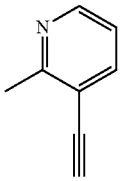
Compound no.	Structure	Alkyne	ESI-MS m/z
Compound 65			531.6 $[M + H]^+$
Compound 66		 Synthesized according to Method J	516.5 $[M + H]^+$
Compound 67		 Synthesized according to Method J	540.3 $[M + H]^+$

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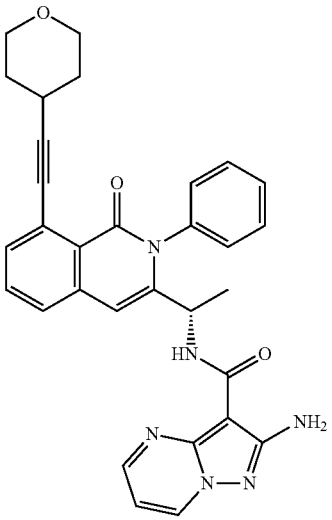
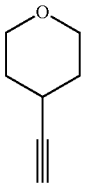
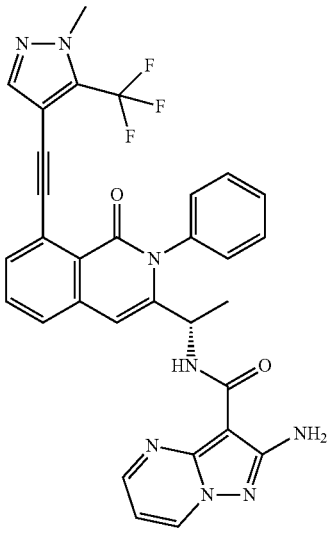
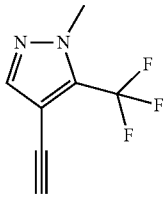
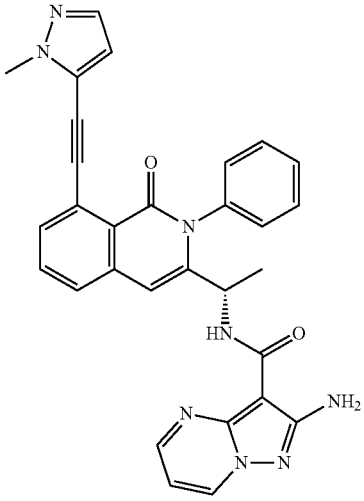
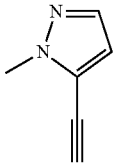
Compound no.	Structure	Alkyne	ESI-MS m/z
Compound 27			533.5[M + H]$^+$
Compound 69		 Synthesized according to Method J	597.2 [M + H]$^+$
Compound 73		 Synthesized according to Method J	529.2 2 [M + H]$^+$

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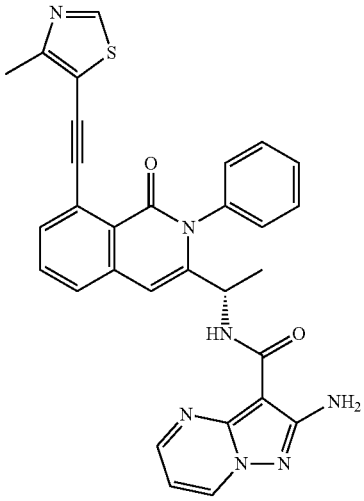
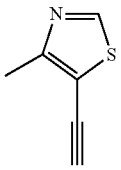
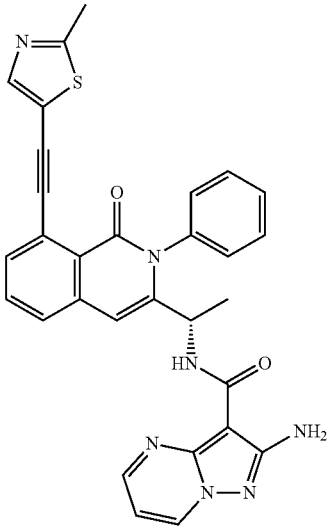
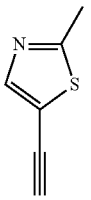
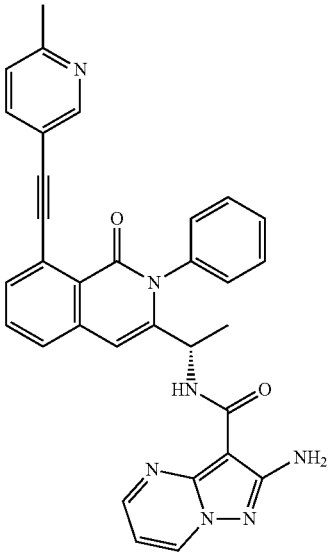
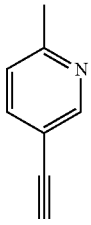
Compound no.	Structure	Alkyne	ESI-MS m/z
Compound 75		 Synthesized according to Method J	546.2 $[M + H]^+$
Compound 76		 Synthesized according to Method J	546.2 $[M + H]^+$
Compound 77		 Synthesized according to Method J	540.3 $[M + H]^+$

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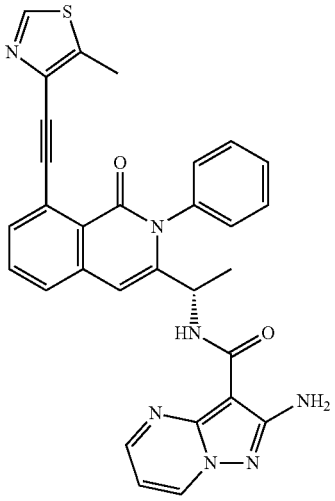
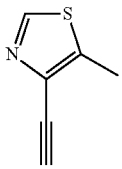
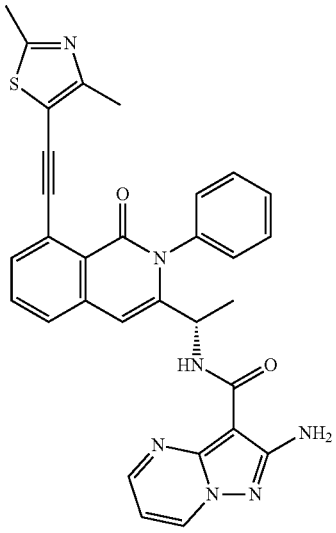
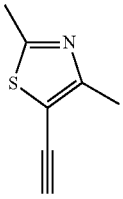
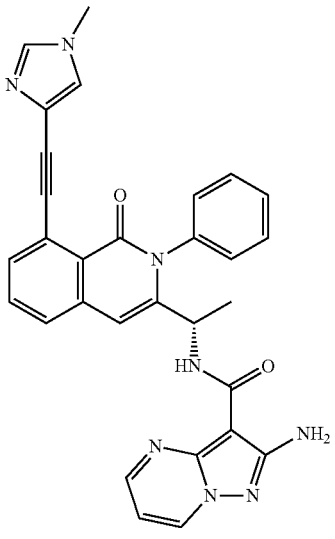
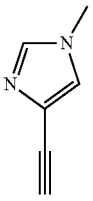
Compound no.	Structure	Alkyne	ESI-MS m/z
Compound 78		 Synthesized according to Method J	546.2 $[M + H]^+$
Compound 79		 Synthesized according to Method J	560.1 $[M + H]^+$
Compound 81		 Synthesized according to Method J	529.0 $[M + H]^+$

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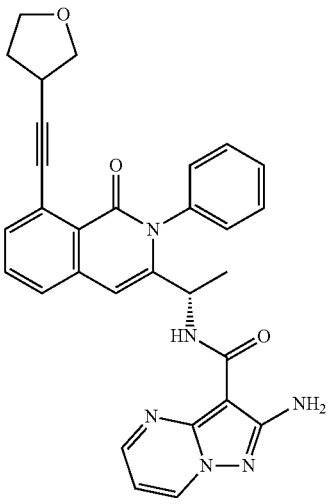
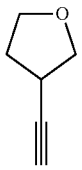
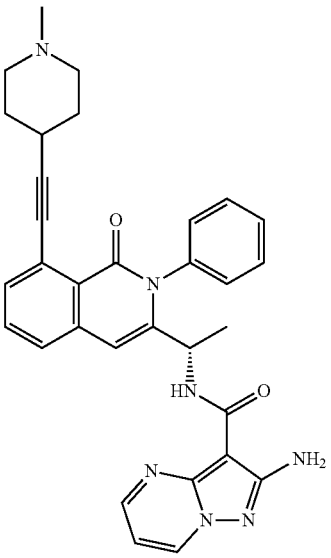
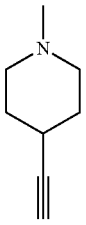
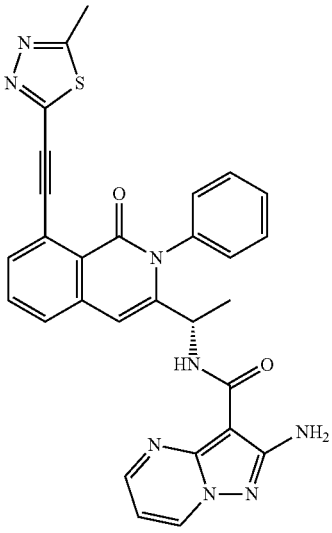
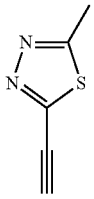
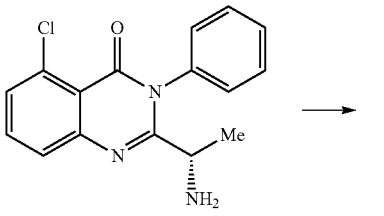
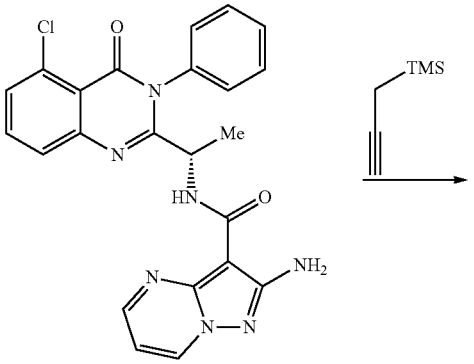
Compound no.	Structure	Alkyne	ESI-MS m/z
Compound 84			519.4 $[M + H]^+$
Compound 85		 Synthesized according to Method J	546.5 $[M + H]^+$
Compound 86		 Synthesized according to Method J	547.0 $[M + H]^+$

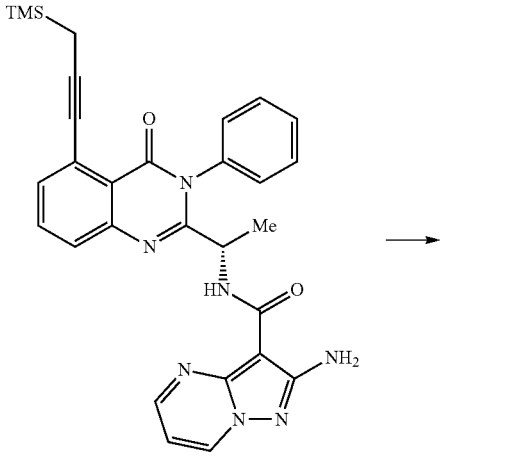
Example 2



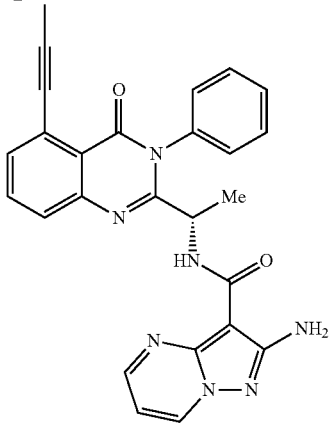
A



AA1



B

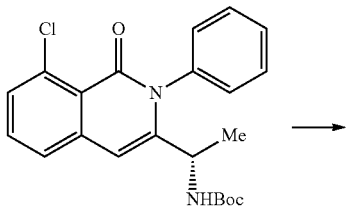


1

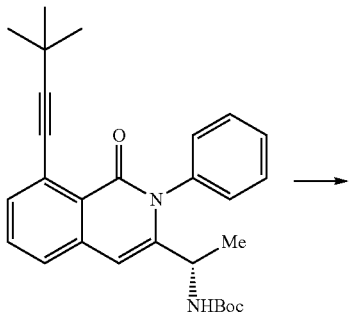
Compound A was prepared according to Method F. It was the converted to compound AA1 using the analogous procedure for compound B in Example 1. Compound 1 was then prepared from compound AA1 in two steps according to the following procedures: Compound AA1 (0.55 mmol, 1.0 equiv), $PdCl_2(MeCN)_2$ (10 mol %), X-Phos (30 mol %) and cesium carbonate (2.6 equiv) were suspended in proprionitrile (4 mL). The mixture was bubbled with Ar for 25 min after which trimethyl(propargyl)silane (1.3 equiv) was added and the reaction was sealed and heated to 90° C. The mixture was allowed to heat for 4.5 h after which it was cooled and partitioned between ethyl acetate and water. The layers were separated and the aqueous layer was extracted with ethyl acetate (2×). The organic layers were combined, dried over sodium sulfate and concentrated onto silica gel (2 g). The crude material was then purified using flash silica gel chromatography (ISCO Combiflash Si-12 g, gradient of 10-55% acetone/methylene chloride) to provide a mixture of compound B and deprotected compound 1.

The mixture (0.23 mmol, 1.0 equiv) was redissolved in anhydrous tetrahydrofuran (6 mL). TBAF in THF (1.0 M, 1.2 equiv) was added and the resulting mixture was stirred at RT for 45 min until complete conversion to compound 1 by TLC analysis. The reaction was then concentrated onto silica gel (1 g) and purified by flash silica gel chromatography (Interchim Si-25 g HP silicycle, gradient of 14-45% acetone/methylene chloride) to provide compound 1. ESI-MS m/z: 464.1 $[M+H]^+$.

Example 3

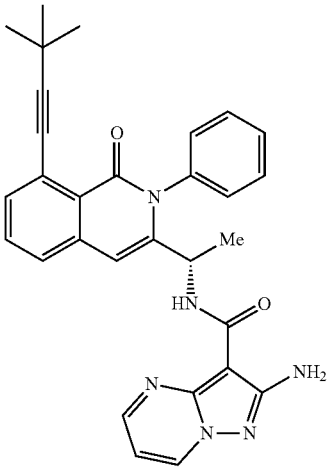


kk



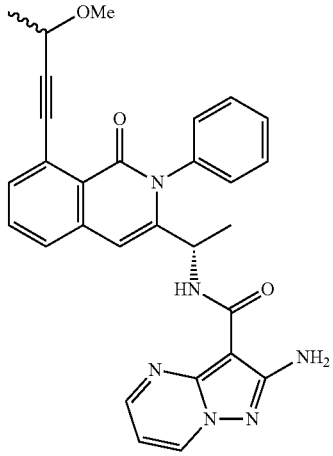
ll

-continued



3

-continued

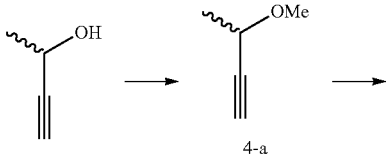


22

Compound kk was prepared from compound A (example 2) under standard Boc protection conditions. It was then converted to compound ll using the analogous coupling procedure for compound B in Example 2 except that 3,3-dimethylbut-1-yne was used in place of triethylsilylacetylene to provide compound ll Compound kk was prepared from compound 1 in analogous fashion to compound gg in Example ZZ. It was then converted to compound ll using the analogous procedure for compound hh in Example ZZ except that 3,3-dimethylbut-1-yne was used in place of triethylsilylacetylene to provide compound ll.

Compound ll (0.094 mmol, 1.0 equiv) was dissolved in anhydrous methylene chloride (2 mL). Trifluoroacetic acid (400 uL, 55 equiv) was added and the reaction was allowed to stir at RT for 2 h until at which point there was no more SM by LC/MS analysis. The reaction was carefully quenched with sodium bicarbonate solution and the aqueous layer was extracted with methylene chloride (2×). The combined organic layers were dried with sodium sulfate and concentrated. The crude material was purified using reverse phase chromatography (Interchim, gradient of acetonitrile and water with 0.1% formic acid) to provide the free amine which was then coupled to 2-((tert-butoxycarbonyl)amino)pyrazolo [1,5-a]pyrimidine-3-carboxylic acid using Method D followed by Boc-deprotection again using the analogous conditions from Example 11 to provide the desired compound 3. ESI-MS m/z: 505.1 $[M+H]^+$.

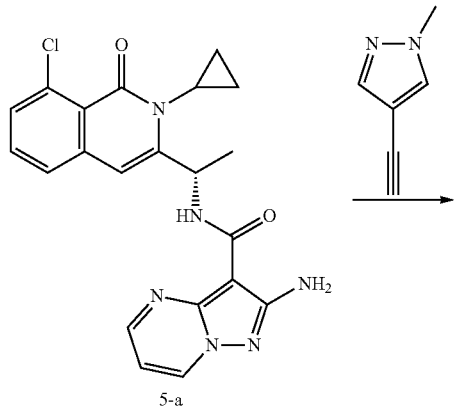
Example 4



4-a

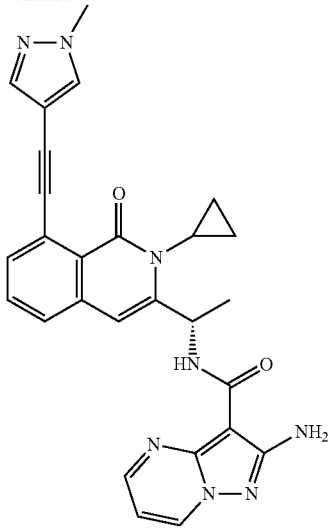
A solution of 3-butyn-2-ol (10 mL, 128 mmol) in N,N-dimethylformamide (20 mL) was added over 30 minutes to a stirred slurry of sodium hydride (60% dispersion in mineral oil, (7.65 g, 2.5 equiv) in N,N-dimethylformamide (100 mL) at 0° C. under an argon atmosphere. After 30 min, dimethyl sulfate (1.5 equiv) was added over 30 min at 0° C. The mixture was then stirred for 30 min at 0° C. after which acetic acid was slowly added (1.05 equiv) and the reaction was allowed to warm to room temperature while stirring for an additional 2 h. The product was isolated from fractional distillation directly from the reaction mixture (58-63° C.) to provided ether 4-a that was used directly in the next step. Compound 4-a was then coupled to compound A using analogous Sonogashira conditions as in to Example 1 to generate compound 22. ESI-MS m/z: 507.5 $[M+H]^+$.

Example 5



5-a

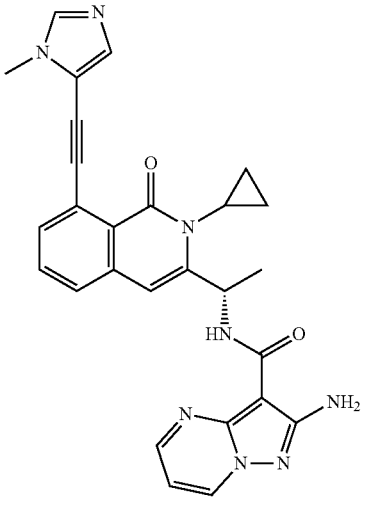
-continued



25

Compound 25 was prepared in analogous fashion to compound B in Example 1. It was then coupled to 4-ethynyl-1-methyl-1H-pyrazole using the Sonogashira conditions in Example 1 to provide compound 25. ESI-MS m/z: 493.4 $[M+H]^+$.

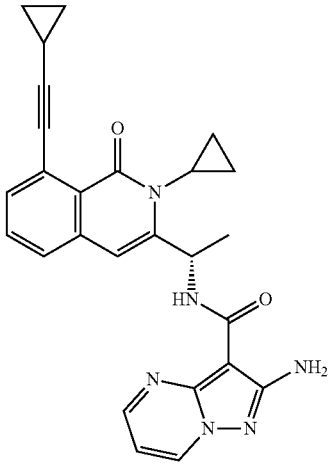
Example 6



23

Compound 23 was prepared in analogous fashion to compound 25 in Example 5 except that 5-ethynyl-1-methyl-1H-imidazole was used in place of 4-ethynyl-1-methyl-1H-pyrazole. ESI-MS m/z: 493.4 $[M+H]^+$.

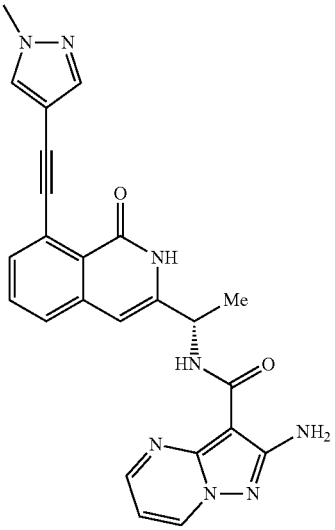
Example 7



24

Compound 24 was prepared in analogous fashion to compound 25 in Example 5 except that ethynylcyclopropane was used in place of 4-ethynyl-1-methyl-1H-pyrazole. ESI-MS m/z: 453.4 $[M+H]^+$.

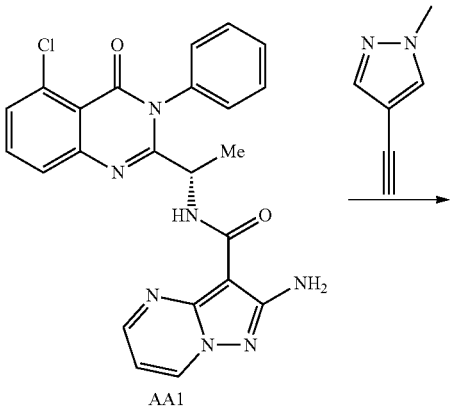
Example 8



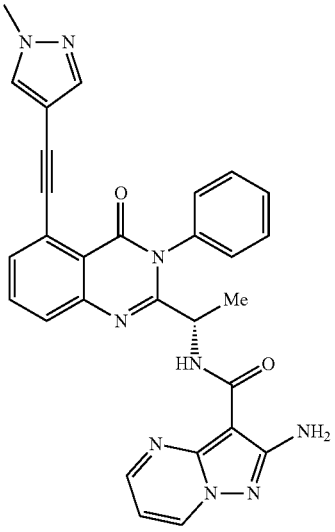
44

Compound 44 was isolated as a byproduct from Example 5. ESI-MS m/z: 453.4 $[M+H]^+$.

Example 9



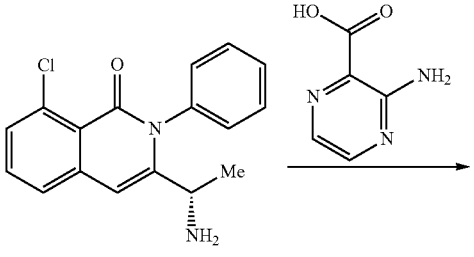
AA1



21

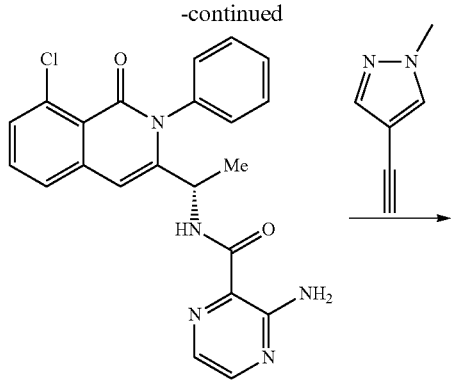
Compound 21 was prepared from compound AA1 using analogous coupling conditions for the preparation of compound 4 in Example 1. ESI-MS m/z: 530.2 $[M+H]^+$.

Example 10

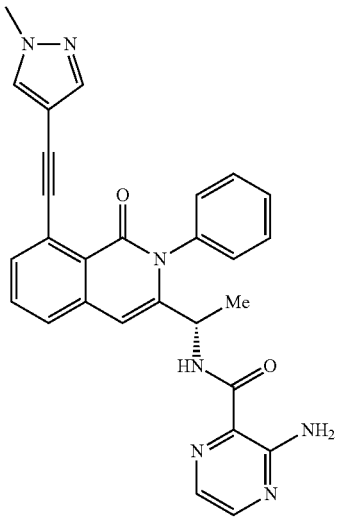


A

-continued



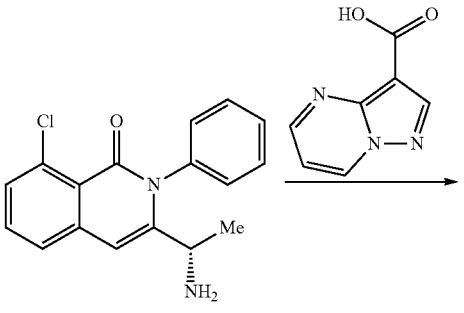
10-a



29

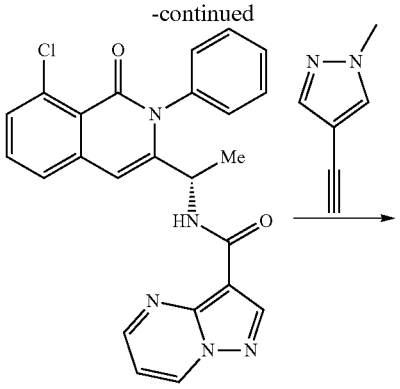
3-Aminopyrazine-2-carboxylic acid was coupled to compound A using Method D to provide compound 10-a. It was then converted to compound 29 using analogous coupling conditions for the preparation of compound 4 in Example 1. ESI-MS m/z: 490.3 $[M+H]^+$.

Example 11

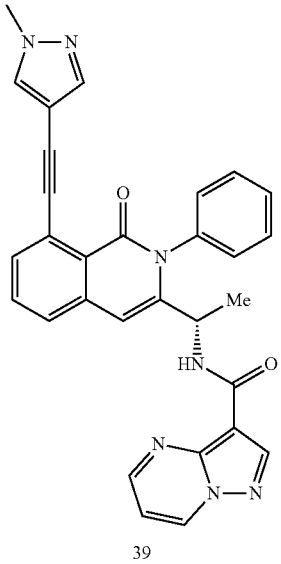


A

-continued



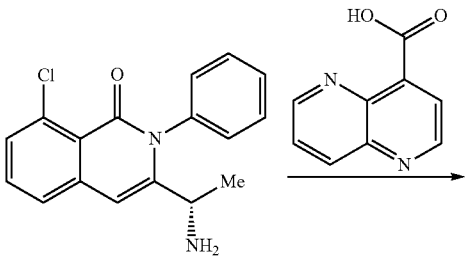
11-a



39

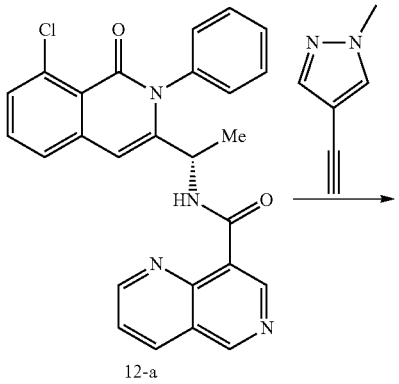
Pyrazolo[1,5-a]pyrimidine-3-carboxylic acid was coupled to compound A using Method D to provide compound 11-a. It was then converted to compound 39 using analogous coupling conditions for the preparation of compound 4 in Example 1. ESI-MS m/z: 514.4 $[M+H]^+$.

Example 12

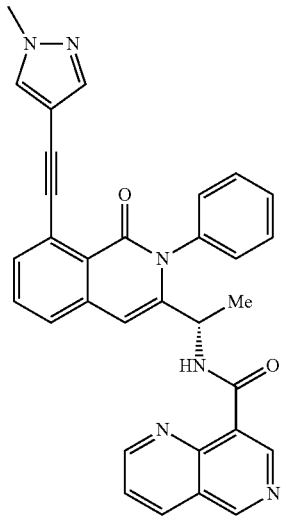


A

-continued



12-a

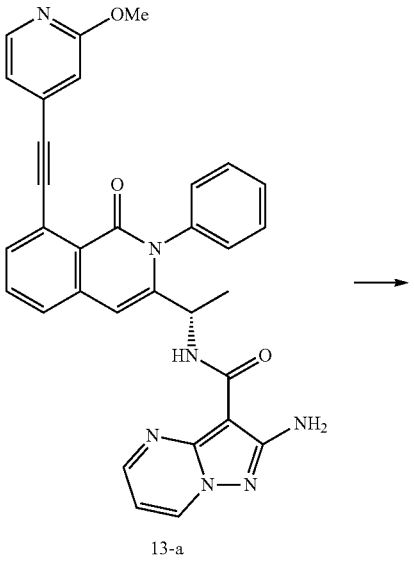


42

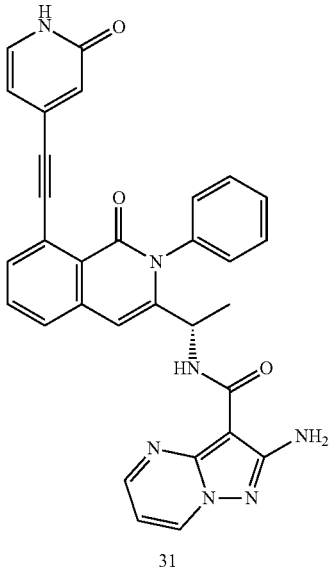
1,5-Naphthyridine-4-carboxylic acid was coupled to compound A using Method D to provide compound 12a. It was

then converted to compound 42 using analogous coupling conditions for the preparation of compound 4 in Example 1. ESI-MS m/z: 525.3 $[M+H]^+$.

Example 13



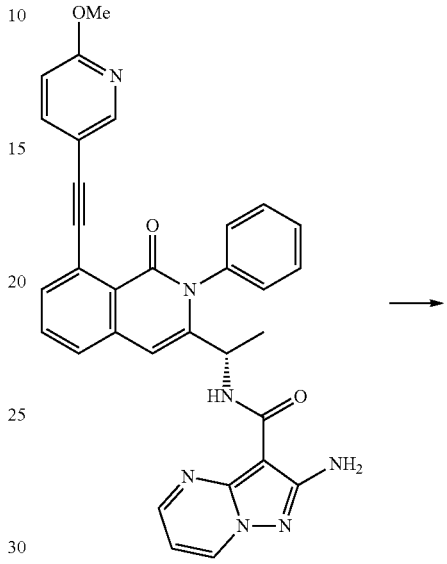
13-a



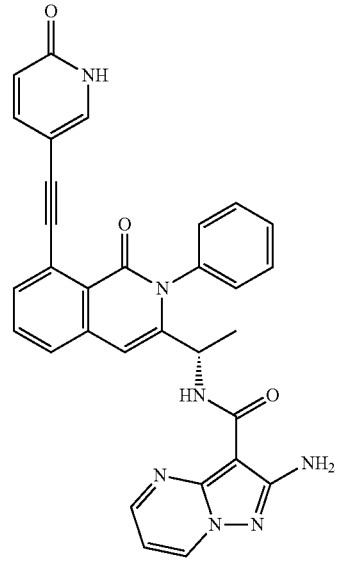
31

Compound 13-a (0.058 mmol, 1.0 equiv) was dissolved in anhydrous acetonitrile (2 mL). Sodium iodide (1.5 equiv) was added followed by TMS-Cl (1.5 equiv) after which point the solution turned to a yellow suspension. The mixture was then heated to 65° C. for 5 h after which there was no more starting material by LC/MS analysis. The reaction was allowed to cool and poured into water (4 mL) and stirred for 15 min after which it was partitioned between water and methylene chloride. The organic layer was when dried and concentrated. The crude material was purified using reverse phase HPLC (Interchim, gradient of 10-90% acetonitrile/water with 0.1% formic acid) to provide desired compound 31. ESI-MS m/z: 542.4 $[M+H]^+$.

Example 14



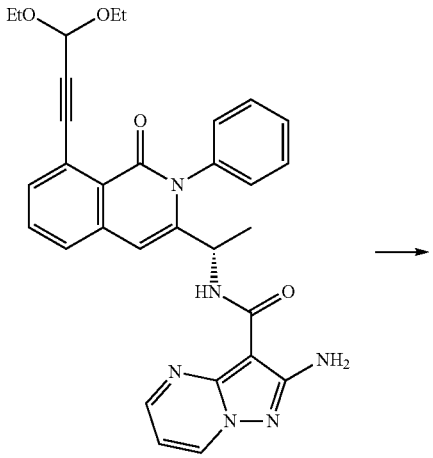
14-a



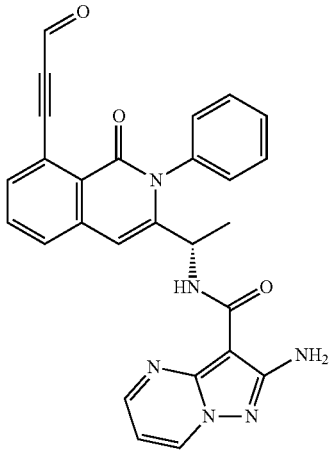
33

Compound 33 was prepared from compound 14-a using the analogous conditions as in Example 13. ESI-MS m/z: 542.4 $[M+H]^+$.

Example 15



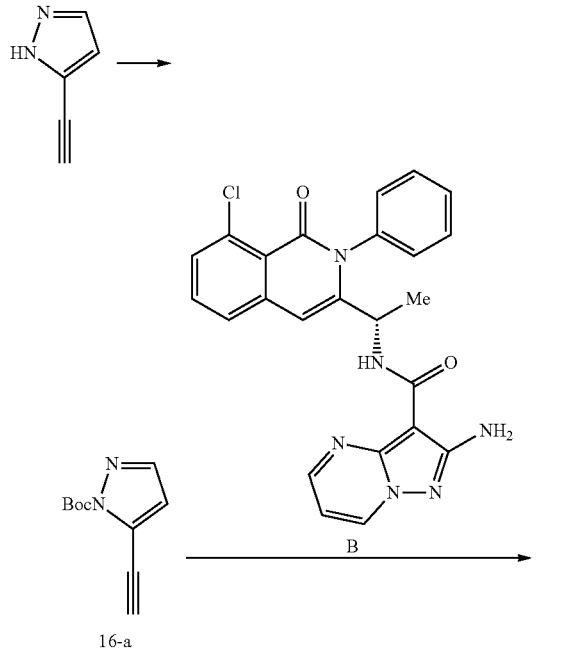
34



36

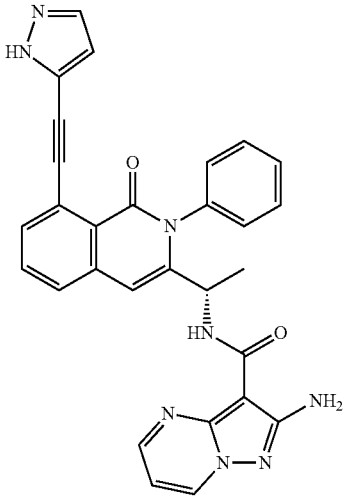
Compound 34 was (0.47 mmol, 1.0 equiv) was dissolved in acetone (5 mL) and water (4 mL). p-Toluene sulfonic acid (25 mol %) was added and the cloudy mixture was heated to 50° C. The mixture was then allowed to cool after which most of the solvent was removed under vacuum. The residue was then partitioned between methylene chloride and saturated sodium bicarbonate. The organic layer was separated and adsorbed onto SiO_2 (3 g) after which it was purified by flash silica gel chromatography (ISCO, 24 g Si column, gradient of 25-100% ethyl acetate/hexanes) to provide the desired aldehyde 36. ESI-MS m/z: 477.2 $[M+H]^+$.

Example 16



16-a

B



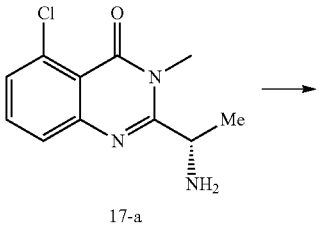
43

5-Ethynyl-1H-pyrazole (1.1 mmol, 1.0 equiv) was dissolved in methylene chloride (10 mL). Triethylamine (3.0 equiv) and Boc anhydride (1.0 equiv) were then added and the reaction was allowed to stir for 2 h. Water (100 mL) was added and the mixture was transferred to a separatory funnel. The layers were separated and the water layer was washed with water (2×20 mL). The organic layers were dried over MgSO4 and concentrated to provide alkyne 16-a which was used directly in the next step.

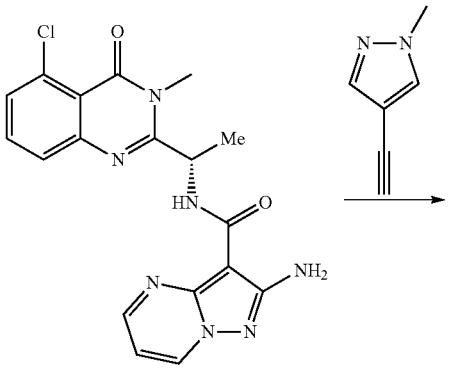
A pressure flask (15 mL) was charged with compound B (0.22 mmol, 1.0 equiv), X-Phos (45 mol %), dichlorobis (acetonitrile)Pd (15 mol %), and cesium carbonate (1.1 equiv) under a flow of N_2. Propionitrile (3 mL) was added and the

solution was bubble with Ar for 1 min. Alkyne 16-a (2.5 equiv) was then added followed by Boc anhydride (1.0 equiv) and the reaction was sealed and heated to 100° C. for 1. h. The reaction was then filtered and concentrated. The residue was redissolved in methylene chloride (3 mL) after which trifluoroacetic acid (800 uL) was added and the mixture was stirred for 1 h. The reaction was then concentrated onto silica gel and purified by flash silica gel chromatography (gradient 0-30% methanol/methylene chloride) to provide compound 43. ESI-MS m/z: 515.4 $[M+H]^+$.

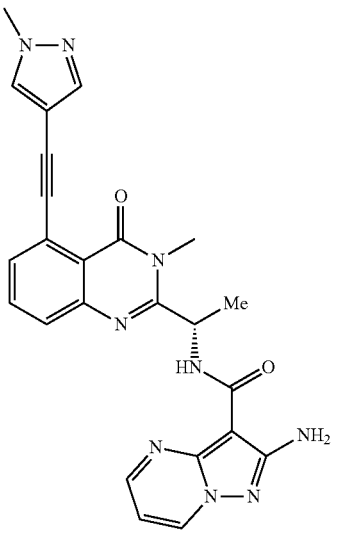
Example 17



17-a



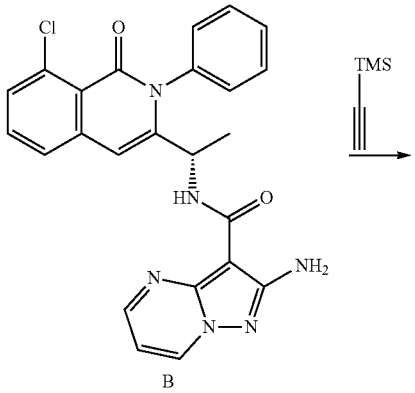
17-b



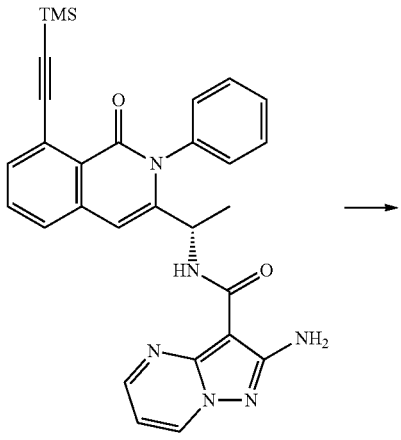
55

Compound 17-a was prepared according to Method F. It was then converted to Compound 55 in analogous fashion to compound 21 in Example 9. ESI-MS m/z: 468.3 $[M+H]^+$.

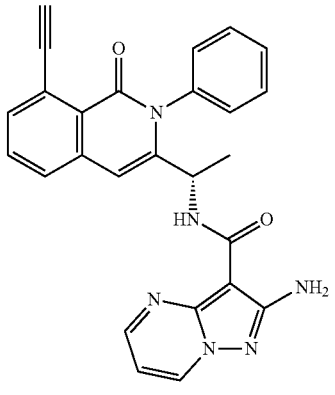
Example 18



B

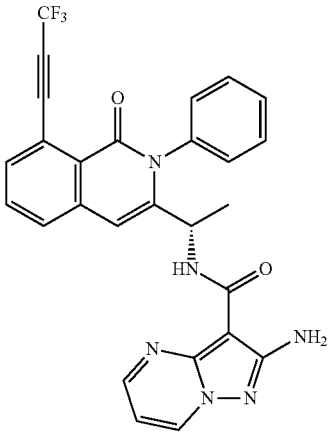


18-a



18-b

-continued



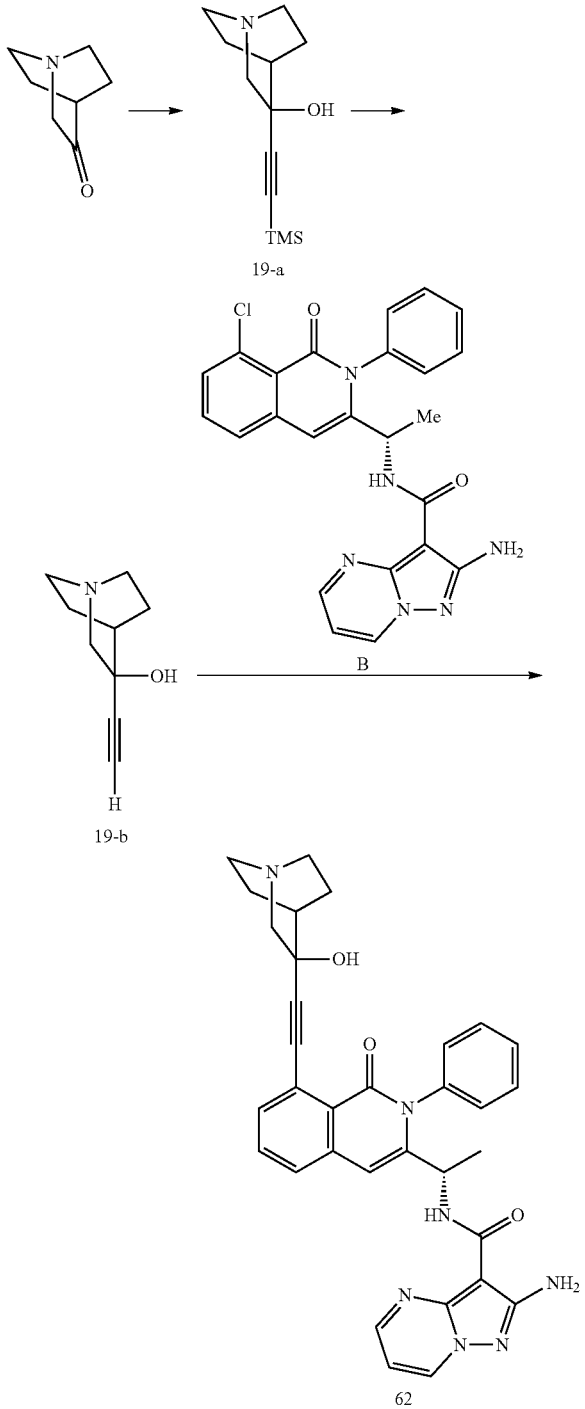
58

A sealed tube (30 mL) was charged with compound B (0.69 mmol, 1.0 equiv), dichlorobis(acetonitrile)palladium (10 mol %), X-Phos (30 mol %) and cesium carbonate (1.5 equiv). Acetonitrile (10 mL) was added followed by the additional of ethynyltrimethylsilane (0.4 mL) and the mixture was purged with Ar for 1 min. The reaction was then sealted and heated in an oil bath to 85° C. After 45 min, an additional aliquot of ethynyltrimethylsilane (1.0 mL) was added and reheated to 75° C. for 14 h after which there was no more starting material by LC/MS analysis. The mixture was filtered and concentrated onto silica gel and purified by flash silica gel chromatography (Combiflash, 12 g column, gradient of 0-5% methanol/methylene chloride) to provide compound 18-a.

Compound 18-a (0.57 mmol, 1.0 equiv) was the dissolved in tetrahydrofuran (4 mL). A solution of TBAF in tetrahydrofuran (0.8 mL, 1.0 M) was added and the mixture was stirred at RT for 1 h at which point the deprotected product was observed as the desired peak by LC/MS analysis. The solution was concentrated onto silica gel and purified using flash silica gel chromatography (Combiflash, 12 g column, gradient of 0-5% methanol/methylene chloride) to provide compound 18-b.

An oven dried RBF with a stir bar was charged with CuI (0.34 mmol, 1.0 equiv), 1,10-phenanthroline (1.0 equiv) and KF (1.0 equiv). Dry N,N-dimethylformamide (2 mL) was added and the mixture was stirred for 15 min under an atmosphere of air. Trimethyl(trifluoromethyl)silane (5.0 equiv) was then added and the mixture was heated to 100° C. under an air atmosphere. A solution of compound 18-b (1.0 equiv in 2 mL N,N-dimethylformamide) was added over the course of 4 h using a syringe pump. Following the completion of compound 18-b addition, the reaction was stirred for an additional 1.5 h at 100° C. At this point the reaction was allowed to cool after which water (100 mL) was added and the mixture was extracted with methylene chloride (3×). The combined organics were washed with water, dried over sodium sulfate and concentrated onto silica gel after which the material was purified by flash silica gel chromatography (Combiflash, 4 g column, gradient of 0-10% methanol/methylene chloride). The crude material was further purified by reverse phase HPLC (Interchim, gradient of 0-10% acetonitrile:water with 0.1% formic acid to provide the desired alkyne 58. ESI-MS m/z: 517.5 $[M+H]^+$.

Example 19



62

3-Quinuclidone hydrochloride (9.6 mmol, 1.0 equiv) was suspended in methylene chloride (30 mL) and potassium carbonate solution was added (1.0 M, 16 ml). The mixture was stirred for 30 min after which the organic later was

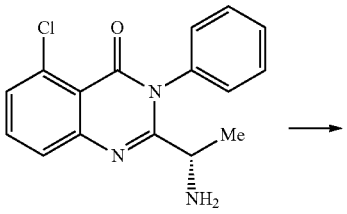
collected and the aqueous layer was washed with methylene chloride (3×20 mL), dried over sodium sulfate, filtered and concentrated to provide the corresponding free base.

A solution of ethynyltrimethylsilane (10.6 mmol, 1.1 equiv) in tetrahydrofuran (10 mL) was cooled to −10° C. n-Butyl lithium (2.5 M in THF, 1.15 equiv) was added over 7 min. The reaction was stirred at −10° C. for 30 min after which it was cooled to −78° C. 3-Quinuclidone (1.0 equiv in 20 mL THF) was added to the flask over a period of 20 min, stirred for 15 additional min after which the cooling bath was removed and the reaction was allowed to stir at 23° C. for 15 h. The mixture was then quenched with saturated ammonium chloride (50 mL) and extracted with ethyl acetate (5×25 mL). The combined organic layers were then washed with water (1×20 mL) and brine (1×20 mL), dried over sodium sulfate and concentrated under reduced pressure to provide alkyne 19-a which was used directly in the next step.

Compound 19-a (7.7 mmol, 1.0 equiv) was dissolved in methanol (17 mL) and treated with potassium carbonate (1.05 equiv). The reaction was allowed to stir at room temperature for 4 h after which it was filtered through celite, washing with 10% methanol in methylene chloride. The filtrates were concentrated under reduced pressure to half the volume and filtered again after which they were concentrated completely under reduced pressure. The material was then redissolved in chloroform (30 mL) and washed with 50% saturated brine (10 mL). The aqueous layer was extracted with chloroform (3×20 mL). The combined organic layers were then washed with brine (5 mL), dried over sodium sulfate and concentrated under reduced pressure to provide compound 19-b.

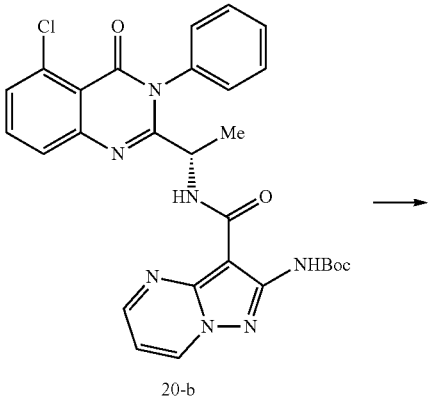
An oven dried sealed tube was charged with dichlorobis (acetonitrile)palladium (15 mol %), X-Phos (45 mol %), and cesium carbonate (1.2 equiv) followed by propionitrile (5 mL). Compound B (0.22 mmol, 1.0 equiv) was added and the reaction was degassed with Ar for 15 min Alkyne 19-b (3.0 equiv) was added as a solid and the mixture was purged for an additional 1 min with Ar. The flask was then sealed and heated to 100° C. for 2.5 h after which there was no more starting material by LC/MS analysis. The mixture was filtered through celite and the filtrate was concentrated under reduced pressure and adsorbed onto a 1:4 ratio of Si-Triamine and silica gel (1.5 g) after which it was purified using flash silica gel chromatography (Interchim, 12 g Si column, gradient of 0-20% 1M ammonia in methanol/methylene chloride) to provide the desired compound 62. ESI-MS m/z: 574.6 $[M+H]^+$.

Example 20

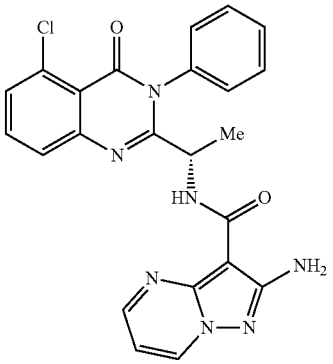


20-a

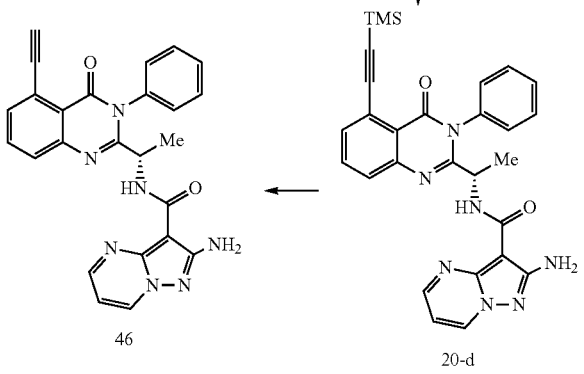
-continued



20-b



20-c



46

20-d

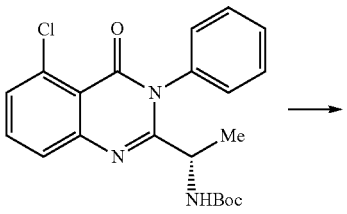
Compound 20-a was prepared according to Method F. It was then coupled to 2-((tert-butoxycarbonyl)amino)pyrazolo [1,5-a]pyrimidine-3-carboxylic acid according to Method D to provide compound 20-b. The Boc group was deprotected under standard conditions using trifluoroacetic acid according to the following procedure: Compound 20-b was dissolved in 0.06 M methylene chloride. Trifluoroacetic acid (40 equiv) was then added and the reaction was allowed to stir at room temperature for 30 min. The mixture was then pourded into saturated sodium bicarbonate solution and extracted with methylene chloride (2×). The combined organic layers were dried over Na_2SO_4, and concentrated to provide compound 20-c which was used directly in the next step.

A vial was then charged with compound 20-c (0.25 mmol, 1.0 equiv), cesium carbonate (3.0 equiv), $PdCl_2(CH_3CN)_2$ (30 mol %), X-Phos (15 mol %), propionitrile (3 mL) and DMSO (0.5 mL). The mixture was bubbled with Argon for 10

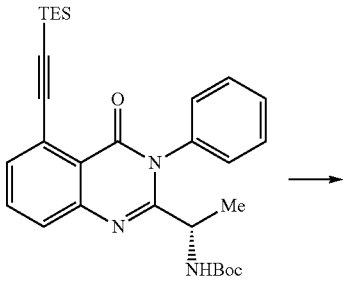
min after which TMS-acetylene (4.0 equiv) was added and the reaction was sealed and heated to 100° C. for 2 h until there was no more starting material as indicated by LC/MS analysis. The reaction was then partitioned between ethyl acetate and brine. The water layer was washed with ethyl acetate (1×). The combined organics were dried over Na_2SO_4 and concentrated to provide crude compound 20-d which was used directly in the next step.

Compound 20-d (0.25 mmol, 1.0 equiv) was dissolved in tetrahydrofuran (10 mL) after which 1M TBAF in tetrahydrofuran (4.0 equiv, 989 uL). Ater 15 min there was no more SM by HPLC analysis. The crude reaction is then partioned between methylene chloride and water. The aqueous layer was first extracted with methylene chloride (2×) and then diluted with 1N HCl and extracted with ethyl acetate (2×). All the organic layers were dried over Na_2SO_4 and concentrated to provide crude material which was first purified by flash silica gel chromatography (Interchim Si-25 g HP silicycle, gradient of 30-100 ethyl acetate/hexanes) to provide material which was further purified by HPLC (30-90% methanol/0.1% trifluoroacetic acid in water) to provide compound 46. ESI-MS m/z: 450.3 $[M+H]^+$.

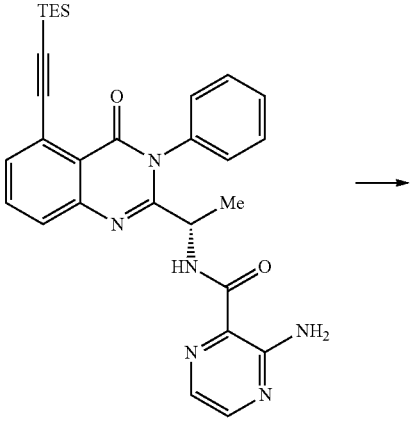
Example 21



21-a

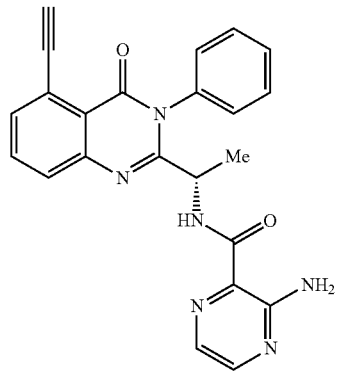


21-b



21-c

-continued

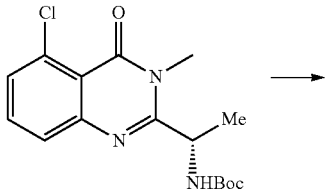


47

Compound 21-a was prepared according to Method F. It was then coupled to TES-acetylene according to the following procedure: A vial was then charged with compound 21-a (0.48 mmol, 1.0 equiv), cesium carbonate (2.6 equiv), $PdCl_2(CH_3CN)_2$ (10 mol %), X-Phos (30 mol %) and acetonitrile (2 mL). The mixture was bubbled with Argon for 10 min after which TES-acetylene (1.3 equiv) was added and the reaction was sealed and heated to 90° C. for 2 h until there was no more starting material as indicated by LC/MS analysis. The reaction was then partitioned between ethyl acetate and brine. The water layer was washed with ethyl acetate (1×). The combined organics were dried over Na_2SO_4 and concentrated provide crude compound 21-b which purified using flash silica gel chromatography (Interchim Si-25 g HP silicycle, gradient of 30-100 ethyl acetate/hexanes).

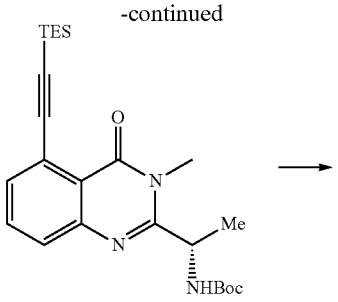
Compound 21-b was then Boc-deprotected and coupled to 3-amino-pyrazine-2-carboxylic acid using Method D to provide compound 21-c. Compound 21-c (0.11 mmol, 1.0 equiv) was dissolved in tetrahydrofuran (4 mL) and treated with 1M TBAF in tetrahydrofuran (3.0 equiv, 320 uL). After 35 min there was no more starting material by LC/MS analysis. The crude mixture was concentrated, pre-adsorbed onto silica gel and purified using flash silica gel chromatography (Interchim Si-12 g HP silicycle, gradient of 40-100 ethyl acetate/hexanes) to provide compound 47 as the desired product. ESI-MS m/z: 411.3 $[M+H]^+$.

Example 22

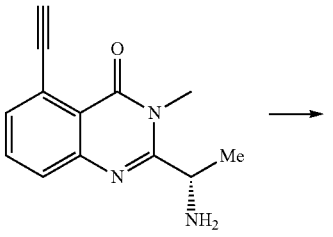


22-a

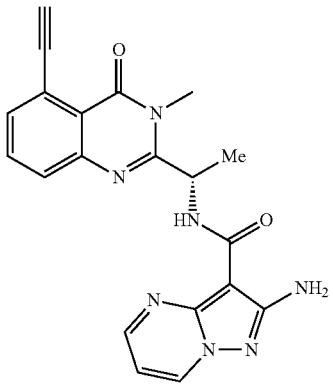
-continued



22-b



22-c

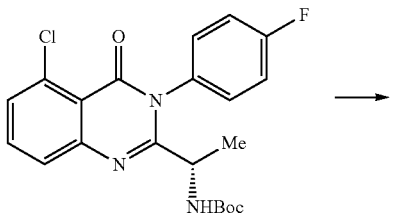


48

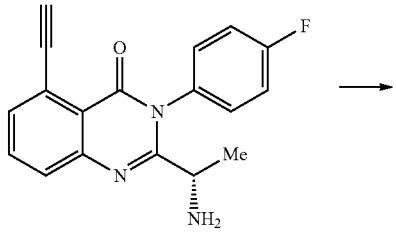
Compound 22-a was prepared according to Method F. A 2 dram vial was then charged with compound 22-a (0.59 mmol, 1.0 equiv), cesium carbonate (2.6 equiv), $PdCl_2(CH_3CN)_2$ (10 mol %), X-Phos (30 mol %) and propionitrile (2 mL). The mixture was bubbled with Argon for 25 min after which TES-acetylene (2.0 equiv) was added and the reaction was sealed and heated to 90° C. for 3 h until there was no more starting material as indicated by LC/MS analysis. The reaction was then partitioned between ethyl acetate and brine. The water layer was washed with ethyl acetate (1×). The combined organics were dried over Na_2SO_4 and concentrated provide crude compound 32 which purified using flash silica gel chromatography (Interchim Si-25 g HP silicycle, gradient of 0-30 ethyl acetate/hexanes) to provide the desired material.

The TES group was removed and then Boc-deprotected provide amine 22-b. This was then coupled to 2-((tert-butoxycarbonyl)amino)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid using Method D followed by Boc-deprotection to provide the desired compound 48. ESI-MS m/z: 388.0 $[M+H]^+$.

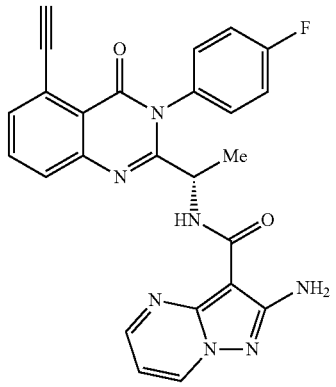
Example 23



23-a



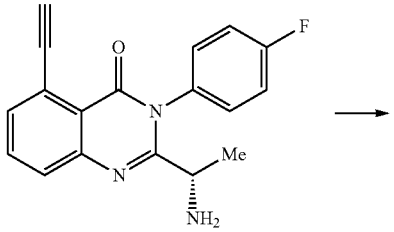
23-b



50

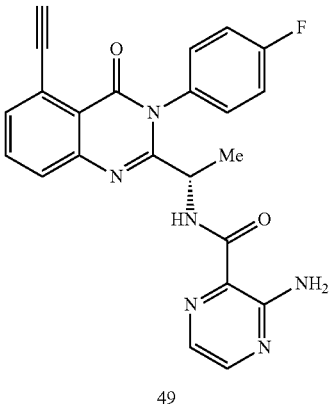
Compound 23-a was prepared according to Method F. It was then converted to amine. This was then coupled to 2-((tert-butoxycarbonyl)amino)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid using Method D followed by Boc-deprotection to provide the desired compound 50. ESI-MS m/z: 478.0 $[M+H]^+$.

Example 24



23-b

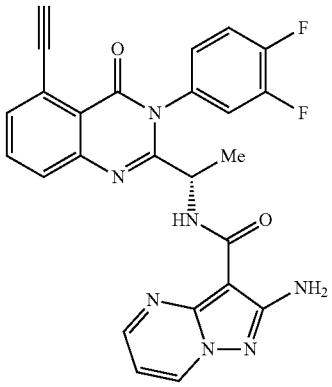
-continued



49

Compound 23-b was coupled to 3-amino-pyrazine-2-carboxylic using Method D to prepare compound 49. ESI-MS m/z: 429.0 $[M+H]^+$.

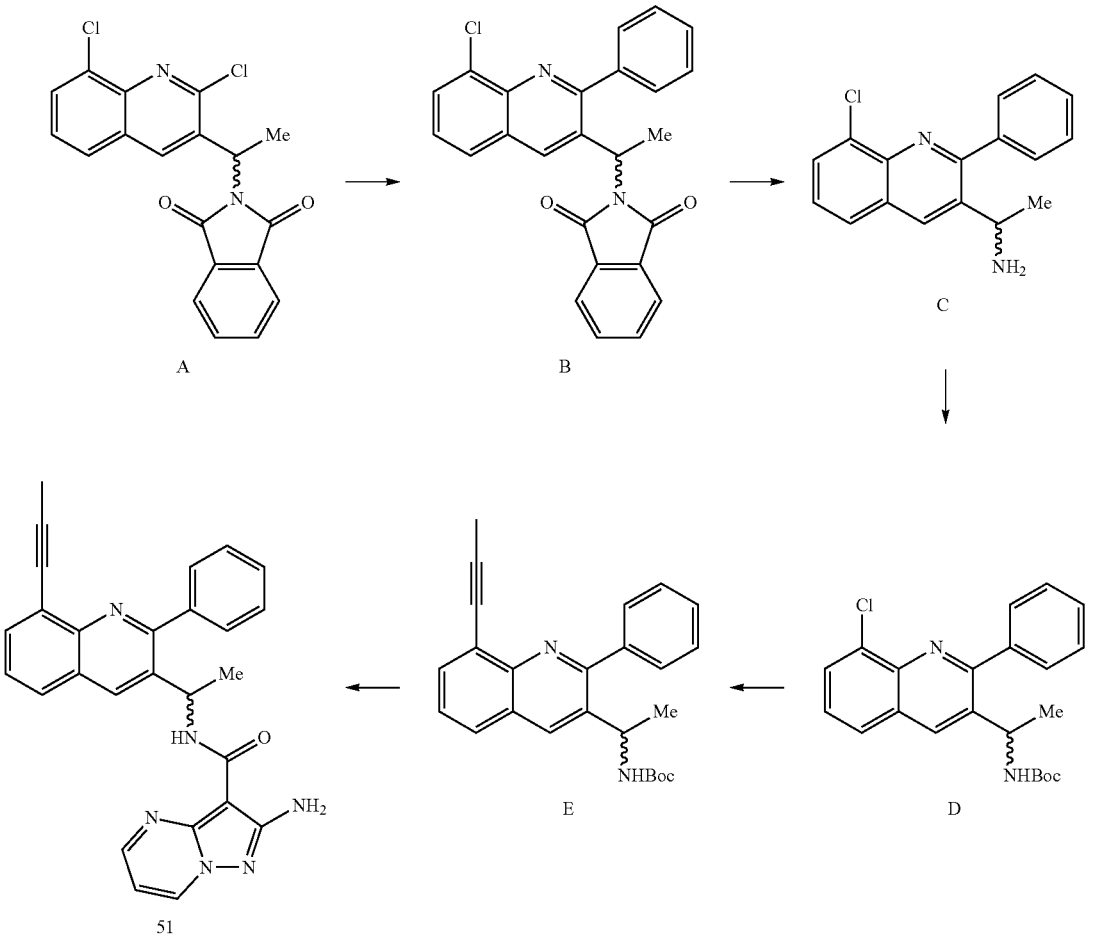
Example 25



45

Compound 45 was prepared in analogous fashion as compound 49, using 3,4-difluoroaniline instead of 4-fluoroaniline and using 2-aminopyrazolo[1,5-a]pyrimidine-3-carboxylic acid instead of 3-amino-pyrazine-2-carboxylic acid. ESI-MS m/z: 486.1 $[M+H]^+$.

Example 26



A

B

C

D

E

51

Compound A was prepared according to WO 2008118468.

A mixture of chloride A (0.93 mmol, 1.0 equiv), phenylboronic acid (1.5 equiv), $Pd(PPh_3)_4$ (5 mol %) and sodium carbonate (2 equiv) in dioxane/water (4/1 v/v, 65 mL) was then degassed with Ar for 10 min. The resulting mixture was heated to 85° C. and stirred for 3 hr. The resulting suspension was cooled to RT, partitioned between ethyl acetate and a saturated aqueous sodium chloride solution. The organic phase was separated, dried with sodium sulfate, pre-adsorbed on silica gel and purified using silica gel chromatography with ethyl acetate and hexanes to afford compound B. ESI-MS m/z: 413.3 $[M+H]^+$.

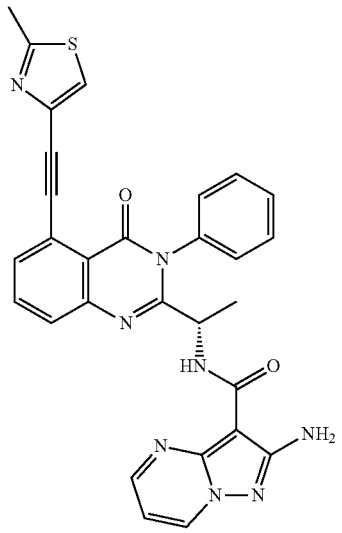
A mixture of phthalimide B (0.56 mmol, 1.0 equiv) and hydrazine (20 equiv) in methanol (10 mL) was heated to 75° C. and stirred for 1 hr. The resulting mixture was concentrated, re-suspended in methylene chloride and filtered. The filtrate was concentrated to dryness to afford compound C. ESI-MS m/z: 283.3 $[M+H]^+$.

Compound C (1.3 mmol, 1.0 equiv) was dissolved in N,N-dimethylformamide (5 mL) and charged with Hunig's base (2.0 equiv) and Boc anhydride (1.1 equiv). The mixture was stirred at RT for 1 h after which there was no more starting material by HPLC analysis. The reaction was then poured into brine and extracted with ethyl acetate. The organic layer as washed with brine, dried over sodium sulfate and pre-adsorbed onto silica gel (2 g). The residue was then purified using flash silica gel chromatography (Interchim, Si-25 g, gradient of 10-30% ethyl acetate/hexanes) to provide compound D. ESI-MS m/z: 383.1 $[M+H]^+$.

Compound D (0.52 mmol, 1.0 equiv) was added to a 25 mL RBF containing a suspension of $PdCl_2(MeCN)_2$ (15 mol %), X-Phos (45 mol %) and cesium carbonate (3.0 equiv) in propionitrile (5 mL). The mixture was stirred for 1 min after which TMS-propargylsilane (3.0 equiv) was added. The mixture was then stirred at RT for 30 min followed by heating to 95° C. for 1 h. LC/MS analysis showed conversion of the starting material to primarily compound E after which the reaction was allowed to cool. It was then partitioned between ethyl acetate and water in a separatory funnel. The layers were separated and the aqueous layer was extracted with ethyl acetate (1×). The combined organic layers were dried with sodium sulfate and pre-adsorbed onto silica gel (2 g). The resulting material was purified using flash silica gel chromatography (ISCO, 25 g column, gradient of 10-30% ethyl acetate/hexanes) to provide alkyne E. ESI-MS m/z: 387.1 $[M+H]^+$.

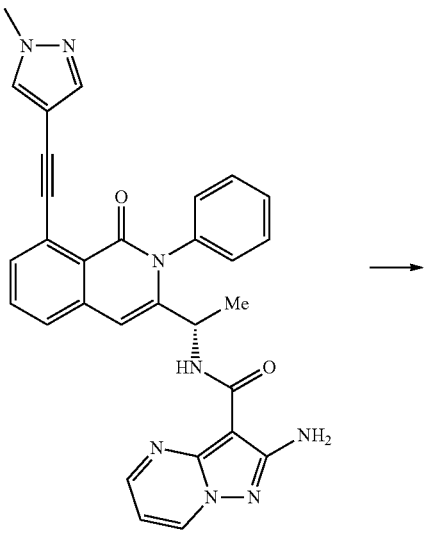
Compound E was then Boc deprotected according to the following procedure: Compound E (0.19 mmol, 1.0 equiv) was dissolved in methylene chloride (4 mL) followed by the addition of trifluoroacetic acid (1 mL). The reaction was allowed to stir at RT for 90 min after which there was complete conversion of starting material by HPLC analysis. The reaction was quenched with saturated sodium bicarbonate solution and extracted with methylene chloride. The organic layer was concentrated over sodium sulfate and concentrated. The resulting amine was then converted to compound 51 using the analogous procedures for the conversion of compound A to B in Example 1. ESI-MS m/z: 447.1 $[M+H]^+$.

Example 27



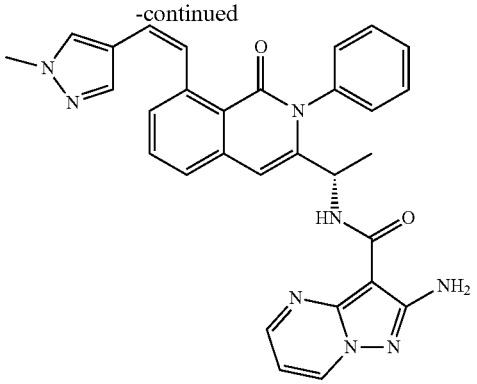
Compound 63 was prepared in analogous fashion to compound 4 in Example 1 except that compound AA1 was used as starting material. ESI-MS m/z: 547.2 $[M+H]^+$.

Example 28



4

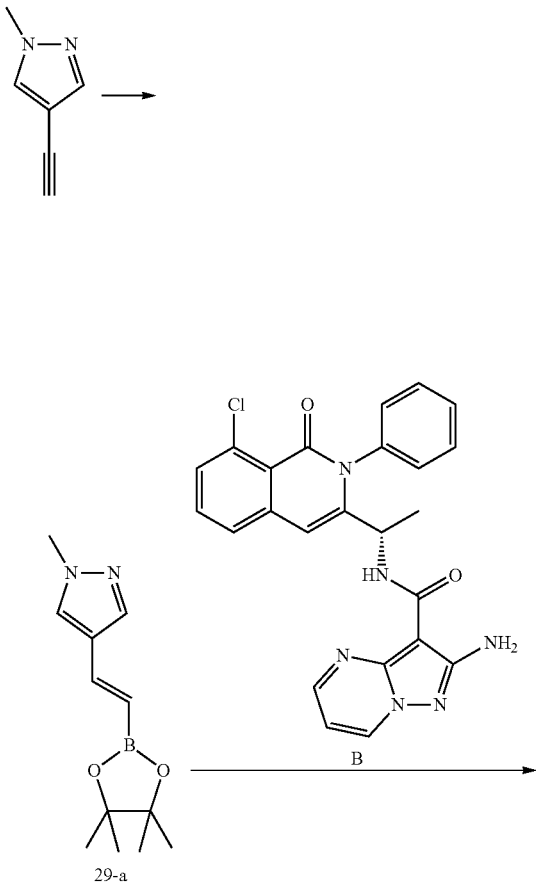
-continued



53

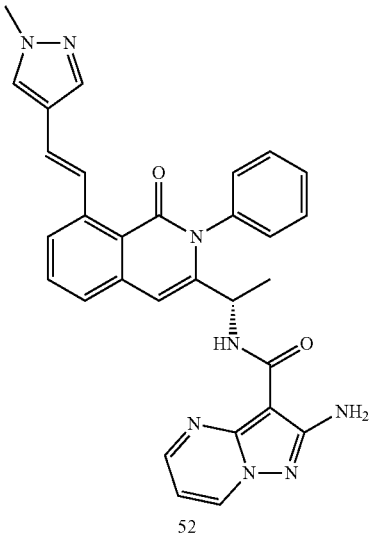
Compound 4 (0.12 mmol, 1.0 equiv) was dissolved in a mixture of ethanol and ethyl acetate (20 mL, 3:1 v/v). Palladium on carbon (19 mg, 10% Pd) was added and the reaction was placed under an atmosphere of H_2. The mixture was stirred at RT for 41 h after which it was filtered through a filter disk, concentrated and purified by flash silica gel chromatography (Combiflash, 4 g Si column, gradient of 0-5% methanol/methylene chloride) to provide alkene 53. ESI-MS m/z: 531.6 $[M+H]^+$.

Example 29



29-a

-continued



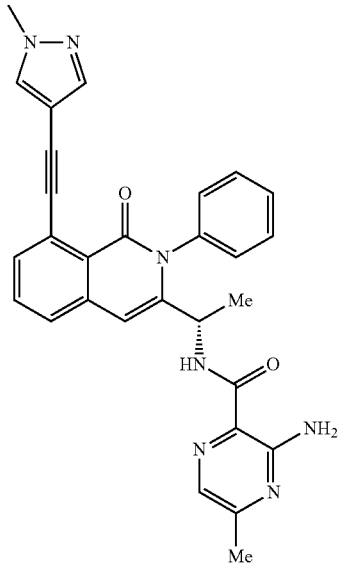
52

4-Ethynyl-1-methyl-1H-pyrazole (1.8 mmol, 1.0 equiv) and pinacolborane (5.0 equiv) were combined in toluene (8 mL) in a RBF under Ar. Carbonylchlorohydridotris(triphenylphosphine)ruthenium(II) (10 mol %) was added and the reaction was heated to 50° C. for 1.5 h after which there was no more starting material by LC/MS analysis. The solvent was evaporated and the crude residue was transferred to a separatory funnel with ethyl acetate (10 mL) and washed with saturated sodium bicarbonate (10 mL), water (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, concentrated and purified using flash silica gel chromatography (gradient 10-40% ethyl acetate/hexanes) to provide alkene 29-a.

Compound B (0.22 mmol, 1.0 equiv), $PdCl_2(Amphos)_2$ (10 mol %) and sodium carbonate (2.0 equiv) were charged to a 4 mL vial under an Ar atmosphere. A solution of compound 29-a in dioxane/water (1.5 equiv, 2 mL solvent, 4:1 v/v) was added and the reaction was stirred at RT for 5 min under Ar before heating to 85° C. for 1 h. The reaction was then allowed to cool, diluted with methylene chloride (15 mL) and washed with water (15 mL). The aqueous layer was then washed with additional methylene chloride (2×15 mL). The organic layers were combined and then washed with water (30 mL), brine (20 mL), dried over sodium sulfate and concentrated to provide crude material which was first purified by flash silica gel chromatography (Interchim Si-12 g, gradient of 0-5% methanol/methylene chloride) followed by purification using

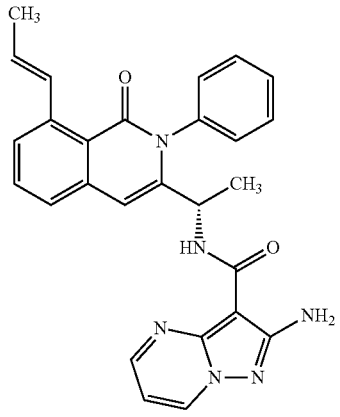
reverse phase HPLC (Interchim C18-Sunfire column, acetonitrile/water/0.1% formic acid) to provide compound 52. ESI-MS m/z: 531.4 $[M+H]^+$.

Example 30



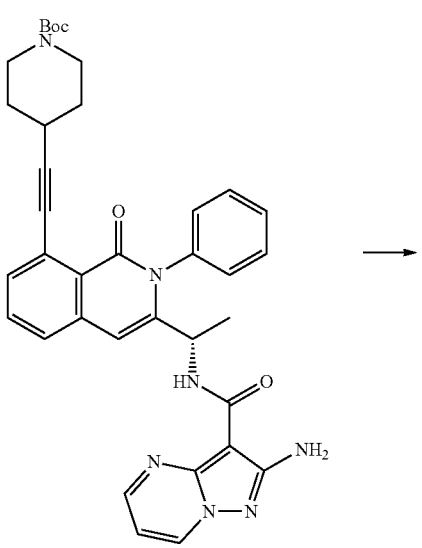
Compound 68 is prepared according to the methods described herein. ESI-MS m/z: 504.2 $[M+H]^+$.

Example 31

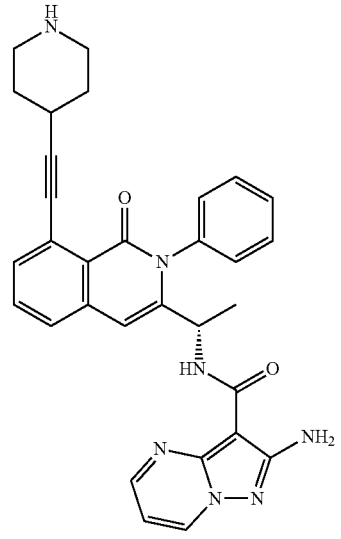


Compound B and trans-1-propen-1-ylboronic acid were coupled using the analogous Suzuki coupling conditions in Example 29 to provide Compound 70. ESI-MS m/z: 465.2 $[M+H]^+$.

Example 32



32a

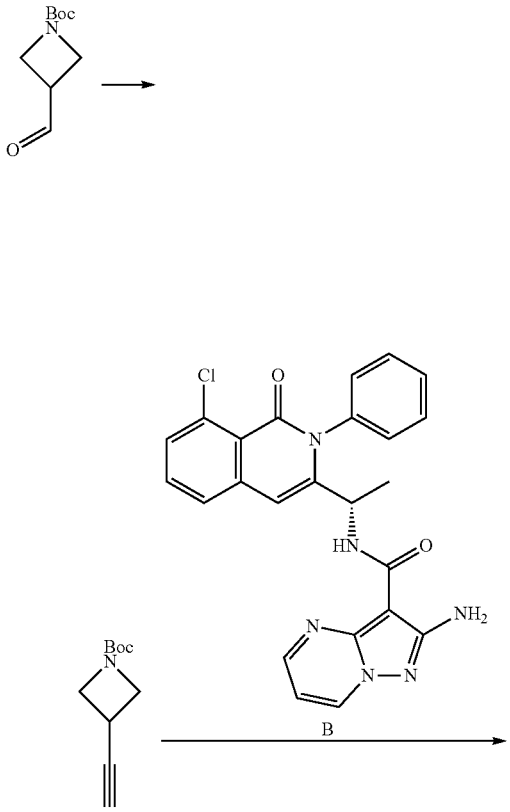


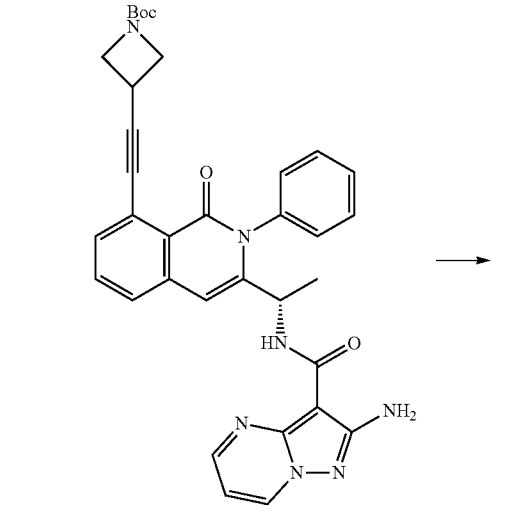
72

Compound B and 4-ethynylpiperidine-1-carboxylic acid tert-butyl ester were coupled using the Sonogashira coupling conditions in Example 1 to provide compound 32a. Compound 32a was then dissolved in methylene chloride (0.007 M) followed by the addition of trifluoroacetic acid (10 equiv). The reaction was allowed to stir for 2 h at RT after which it was concentrated under vacuum. The residue was treated with excess saturated sodium bicarbonate. The resulting residue

was isolated via vacuum filtration and washed with excess water to provide Compound 72. ESI-MS m/z: 532.6 $[M+H]^+$.

Example 33





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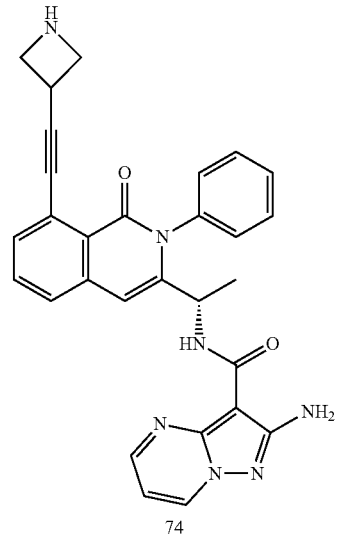
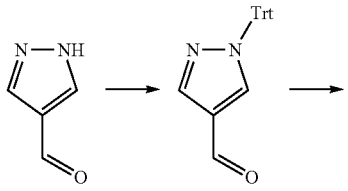
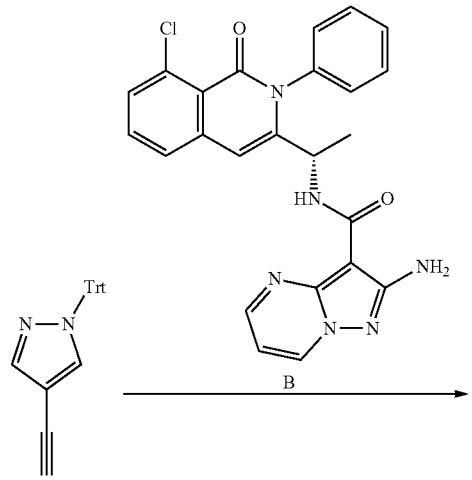


74

Compound 74 was prepared in 3 steps according to the following procedures: tert-Butyl 3-formylazetidine-1-carboxylate was converted to tert-butyl 3-ethynylazetidine-1-carboxylate according to Method J. It was then coupled to compound B and subsequently deprotected in analogous fashion to the synthesis of Compound 72 in Example 32. ESI-MS m/z: 504.5 $[M+H]^+$.

Example 34





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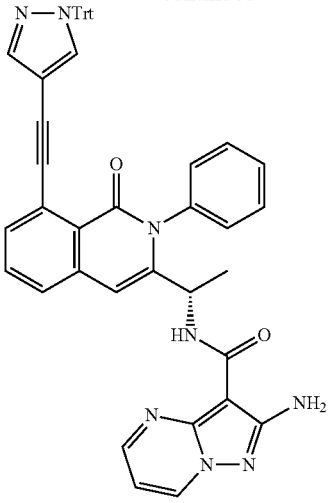
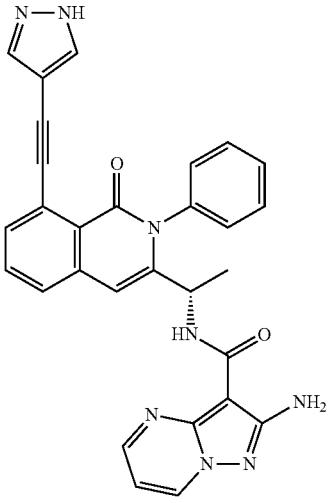
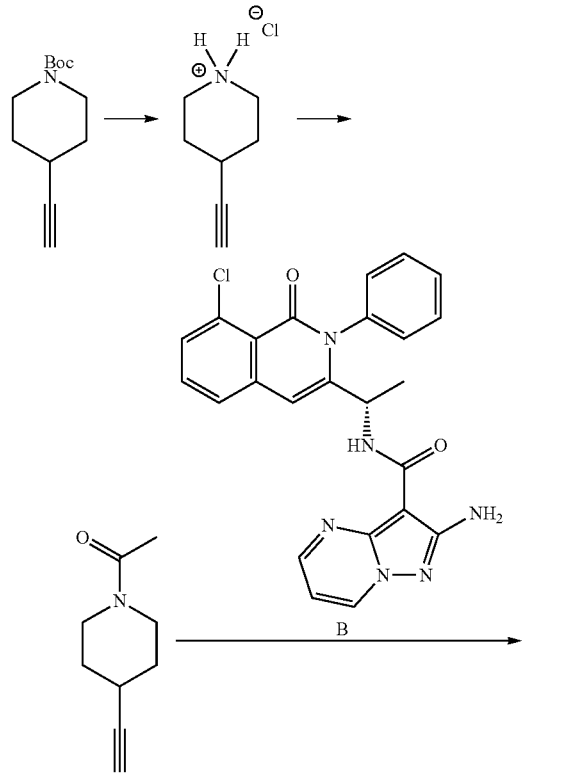


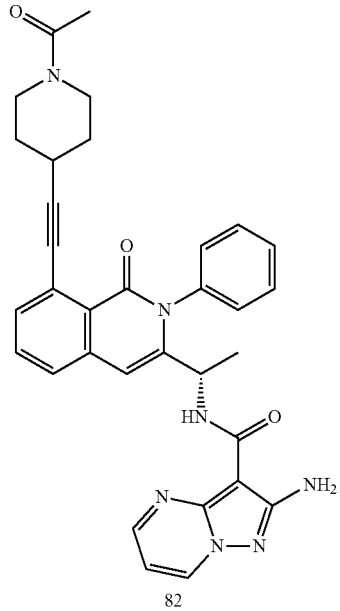


80

Compound 80 was prepared in 4 steps from 1H-pyrazole-4-carbaldehyde according to the following procedures: 1H-pyrazole-4-carbaldehyde (2.1 mmol, 1.0 equiv) was dissolved in 20 mL methylene chloride followed by the addition of triethylamine (3.0 equiv) and trityl chloride (1.0 equiv). The reaction was stirred at RT for 1 h after it was quenched with water (1 mL) and extracted with methylene chloride. The organic layers were concentrated and purified using flash silica gel chromatography (gradient 0-30% methanol/methylene chloride with 0.5% triethylamine). 1-Trity-1H-pyrazole-4-carbaldehyde was then converted to it's corresponding alkyne using Method J after which it was coupled to compound B using the analogous coupling conditions in Example 1. The resulting compound was then deprotected under standard triflouroacetic acid in methylene chloride deprotection conditions after which it was concentrated and purified using flash silica gel chromatography (ISCO, gradient 0-5% methanol/methylene chloride with 0.05% triethylamine and then repurified using reverse-phase HPLC (Interchim C18-Sunfire column, gradient of acetonitrile/water with 0.01% formic acid) to provide compound 80. ESI-MS m/z: 515.0 $[M+H]^+$.

Example 35



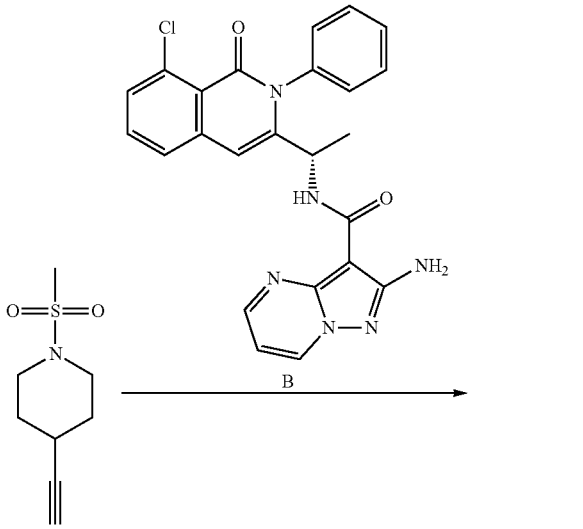


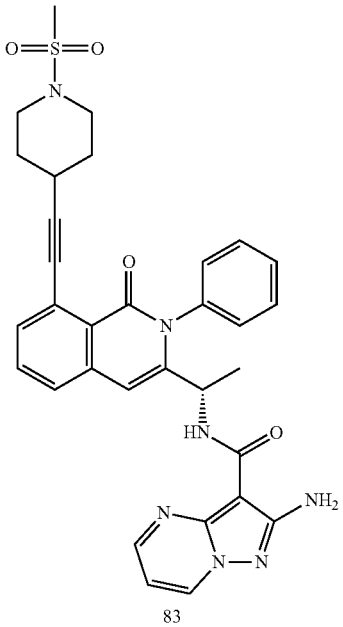
82

Compound 82 was prepared in 3 steps according to the following procedures: N-Boc-4-ethynylpiperidine (3.8 mmol) was dissolved in dioxane (10 mL) and HCl in dioxane (4M, 5.0 equiv) was added. The reaction was allowed to stir at RT for 22 h. The mixture was concentrated under reduced pressure, diluted with 10 mL dioxane and reevaporated under reduced pressure. Diethylether (20 mL) was then added and

the mixture was reevaporated to provide the HCl salt that was used directly in the next step. A suspension of the HCl salt (1.05 mmol, 1.0 equiv) in methylene chloride (1 mL) was cooled to 0-5° C. in an ice bath. Hunig's base (3.0 equiv) was added and then after a minute of stirring acetic anhydride (2.0 equiv) was added. The mixture was allowed to stir for 1 h after which there was no more starting material by TLC analysis. The reaction was then diluted with methylene chloride (5 mL), washed with 5% citric acid (1×2 mL), water (1×2 mL) dried over sodium sulfate, and evaporated under reduced pressure. The crude residue was purified using flash silica gel chromatography (ISCO, 4 g column, 0-50% ethyl acetate in methylene chloride) to provide N-acetyl-4-ethynylpiperidine which was coupled directly to compound B using the analogous Sonogashira coupling conditions in example 1 to provide compound 82. ESI-MS m/z: 574.5 $[M+H]^+$.

Example 36

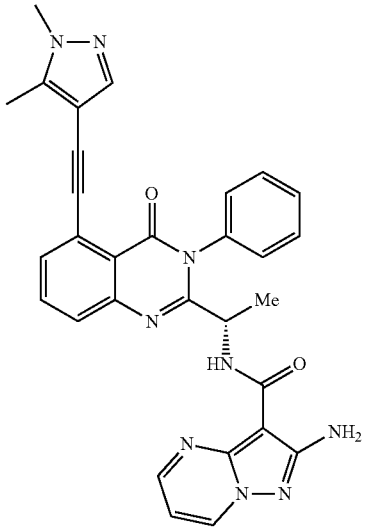




83

A suspension of 4-ethynyl piperidine HCl (1.1 mmol, 1.0 equiv) was suspended in methylene chloride (1 mL) and cooled to 0-5° C. in an ice bath. Hunig's base (3.0 equiv) was added and then after a minute of stirring methanesulfonyl chloride (2.0 equiv) was added and the reaction was allowed to stir for 1 h after which there was no more starting material by LC/MS analysis. The mixture was then diluted with methylene chloride (5 mL) washed with 5% citric acid (1×2 mL), water (1×2 mL), dried over sodium sulfate and concentrated. The crude residue was purified using flash silica gel chromatography (ISCO, 12 g Si column, gradient of 0-10% ethyl acetate/methylene chloride) to provide N-methane sulfonamide-4-ethynylpiperidine which was coupled directly to compound B using the analogous Sonogashira coupling conditions in example 1 to provide compound 83. ESI-MS m/z: 610.6 $[M+H]^+$.

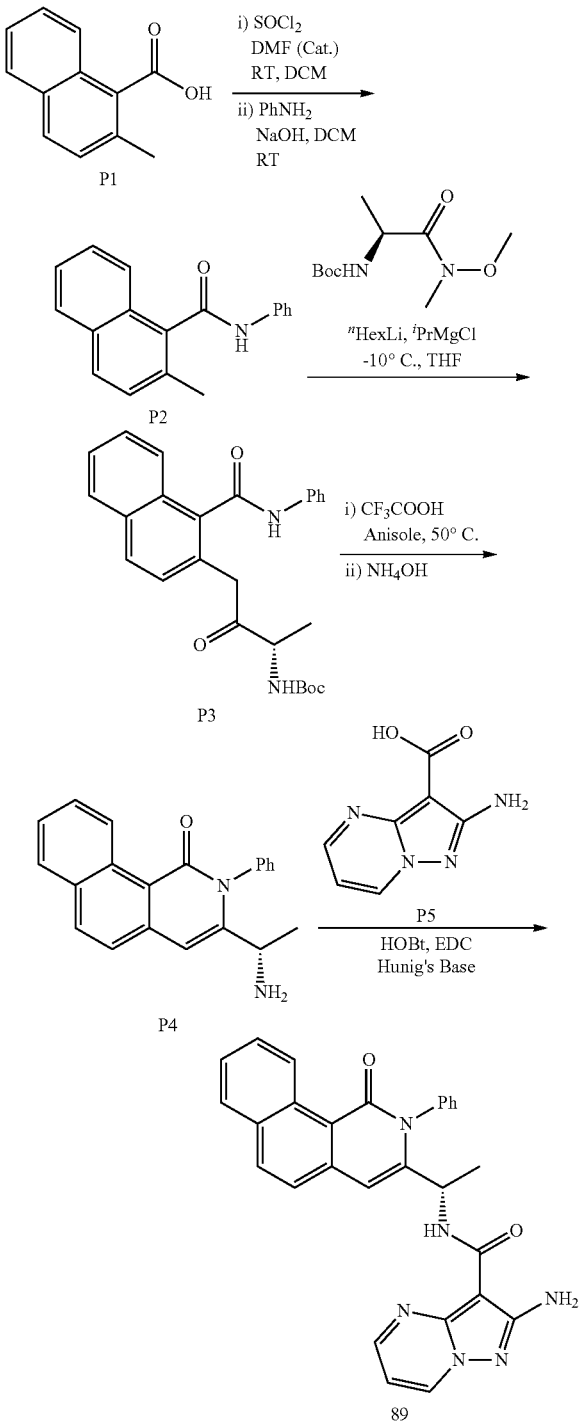
Example 37



Compound 88 was prepared in analogous fashion as compound 21 in example 9 except that 4-ethynyl-1,5-dimethyl-1H-pyrazole was used in place of 4-ethynyl-1-methyl-1H-pyrazole. A suspension of (S)-2-amino-N-(1-(5-chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (146 mg, 0.317 mmol), Cesium carbonate (198 mg, 0.608 mmol, 2 eq.), Dichlorobis(acetonitrile)palladium (II) (15 mg, 0.058 mmol, 0.2 eq.) and Xphos (87 mg, 0.182, 0.6 eq.) in propionitrile (2 mL) was bubbled with argon for 5 minutes. The mixture was charged with 4-ethynyl-1,5-dimethyl-1H-pyrazole (73 mg, 0.6 mmol, 2 eq.), heated to 95° C. and stirred for 2 hr. The resulting mixture was cooled to RT, partitioned between Ethyl acetate and water. The organic phase was separated, washed with saturated aqueous sodium chloride solution, dried with sodium sulfate and concentrated. The residue was purified with silica gel chromatography using a gradient of DCM and MeOH to afford (S)-2-amino-N-(1-(5-((1,5-dimethyl-1H-

pyrazol-4-yl)ethynyl)-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide. ESI-MS m/z: 544.2 $[M+H]^+$.

Example 38



To a stirred mixture of 2-Methyl-1-naphthoic acid 1 (2.5 g, 13.4 mmols) and DMF (0.67 mL) in anhydrous chloroform was added thionyl chloride (1 mL, 13.6 mmols) and the mixture was heated at reflux for 1 h. The solvents were evaporated, dissolved in 10 mL DCM and added to a biphasic mixture of aniline (2.5 mL, 27 mmols) in 40 mL DCM and 40 mL 1M aqueous sodium hydroxide solution. The mixture was stirred for 30 min, the aqueous layer was extracted with DCM (3×20 mL), washed with cold 1M HCl (20 mL), water (3×20 mL), brine (20 mL), dried and the solvents were evaporated under reduced pressure and the crude solid (3.68 g, 92%) was recrystallized from DCM-hexanes to give 1.57 g of pure amide P2. M+H 262.23; M−H 260.23. To a stirred mixture of amide P2 (1.05 g, 1 mmol, 1 eq) in anhydrous THF (8 mL) at −10° C. under an argon atmosphere, a solution of hexyllithium in hexanes (3.93 mL, 9.04 mols, 2.25 eq) was added drop wise over 8 min while keeping the internal temperature between −10° C. and −7° C. The resulting mixture is then stirred at −10° C. for 30 min.

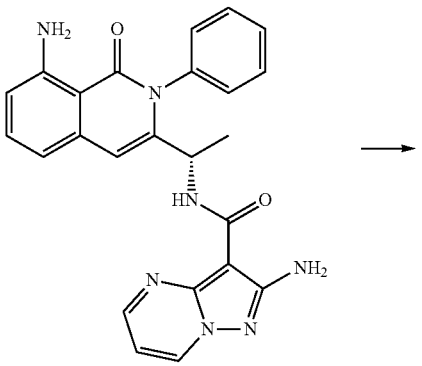
To a stirred mixture of (S)-tert-butyl 1-(methoxy(methyl) amino)-1-oxopropan-2-ylcarbamate (1.12 g, 4.82 mmols, 1.2 eq) in anhydrous THF (8 mL) at −10° C. under an argon atmosphere, a solution of isopropylmagnesium chloride in THF (2.53 mL, 5.06 mmols, 1.26 eq) was added drop wise over 7 min while keeping inner temperature between −10° C. and −7° C. The resulting mixture was stirred at −10° C. for 30 min. This solution was then slowly added to above reaction mixture while keeping inner temperature between −10° C. and −13° C. The resulting mixture is stirred at −10° C. for 1 h and then allowed to warm to room temp over a period of 1 h. The reaction mixture was added into a biphasic mixture of 20 mL 1M citric acid and 30 mL ethyl acetate at −5° C. to 0° C. The aqueous layer was extracted with ethyl acetate (3×20 mL), washed with water and brine (20 mL), dried over sodium sulfate, the solvents were removed in vacuo and the residue was purified by chromatography on silica gel (40 g, 0-50% EtOAc-Hexanes) to give 1.353 g of P3 as a solid. M+H 432.42; M−H 431.43.

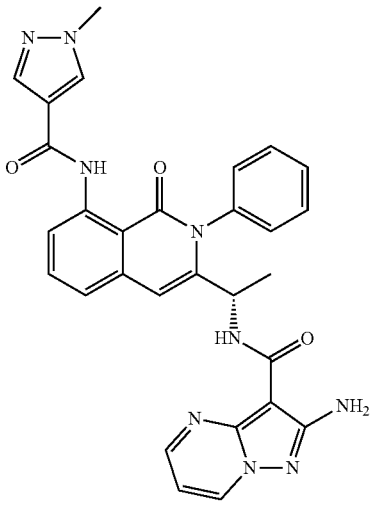
A solution of 3 (1.1 g, 2.54 mmols) in 9 mL anisole was treated with trifluoroacetic acid (1.52 mL, 20.3 mmols) and the mixture was heated at 50 C for 18 h. The mixture was cooled, treated with 25 mL MTBE, the precipitated solids were filtered, washed with MTBE (3×10 mL) and dried to give 1.07 g (2.5 mmols) the TFA salt of P4 as a solid.

200 mg of the TFA salt of 4 (0.467 mmols) was suspended in 6 mL DCM, treated with aqueous ammonium hydroxide solution (2 mL, ~6%) for 30 min. The mixture was diluted with water (10 mL), extracted with DCM (2×5 mL), washed with water (5 mL), dried and the solvents were evaporated in vacuo to give 149 mg (0.467 mmols) of crude P4. The crude P4 (120 mg, 0.382 mmols), 2-Aminopyrazolo[1,5-a]pyrimidinecarboxylic acid (75 mg, 0.42 mmols), HOBt (70 mg, 0.46 mmols), EDC (91 mg, 0.48 mmols) and Hunig's base (0.27 mL, 1.53 mmols) in 3 mL DMF was stirred for 19 h. The mixture was slowly diluted with 6 mL methanol, heated to 50 C and cooled to room temperature. The precipitated solids

was collected, washed with methanol and dried to give 89 as a solid (154 mg). ESI-MS m/z: 475.46 $[M+H]^+$.

Example 39



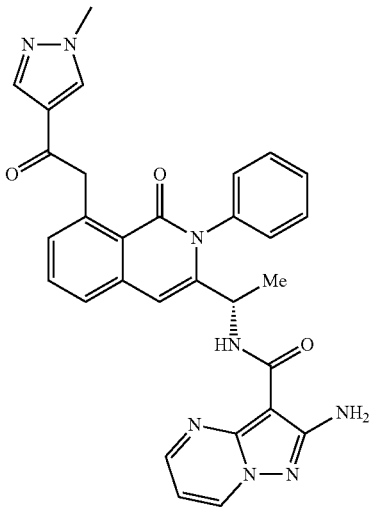
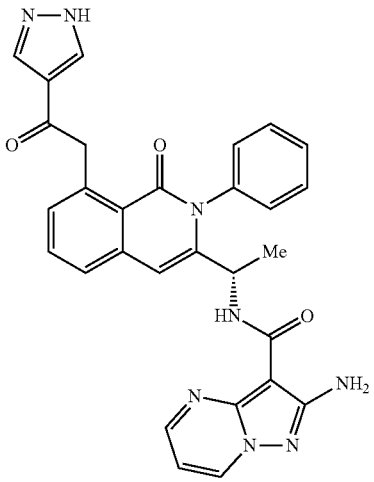


90

Compound 90 was prepared according to amide formation methods generally known in the art. ESI-MS m/z: 548.31 $[M+H]^+$.

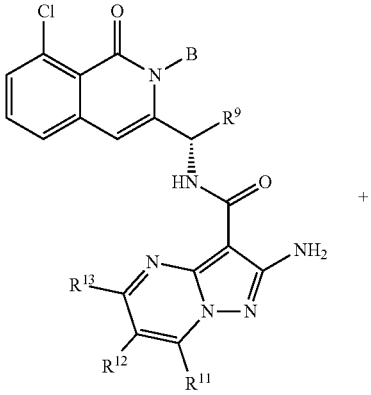
Example 40

Compounds 91 and 92 were prepared.

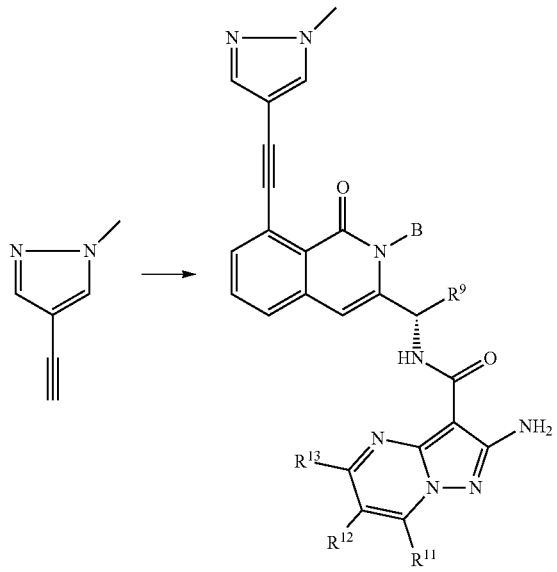
Compound no.	Structure	ESI-MS m/z
Compound 91		547.25 $[M + H]^+$
Compound 92		531.31 $[M + H]^+$

Example 41

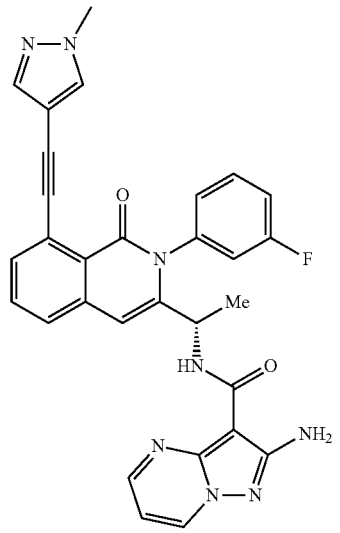
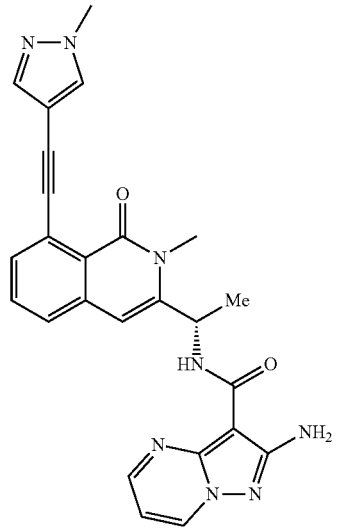
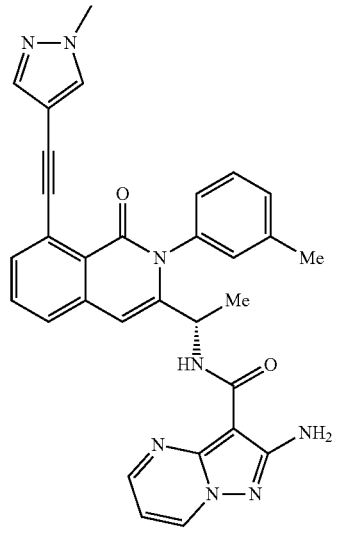
Compounds 93-108 were prepared according to the procedure below.



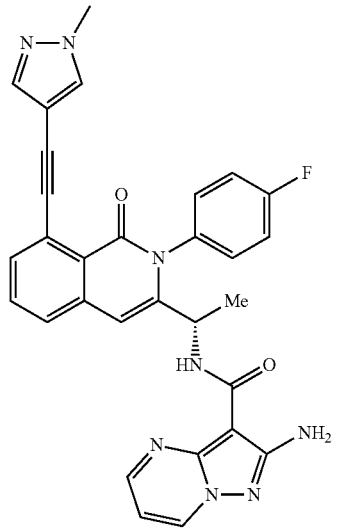
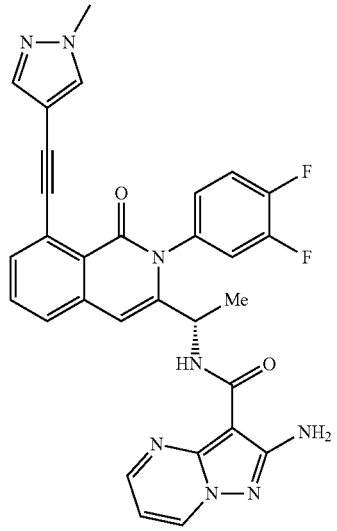
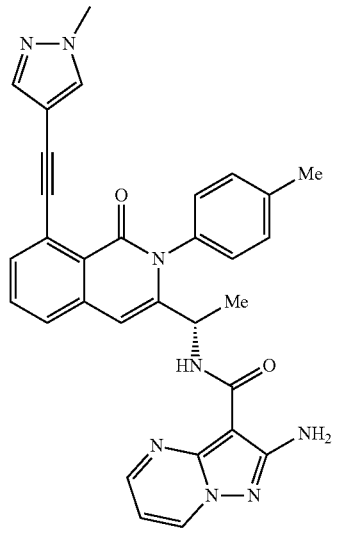
+



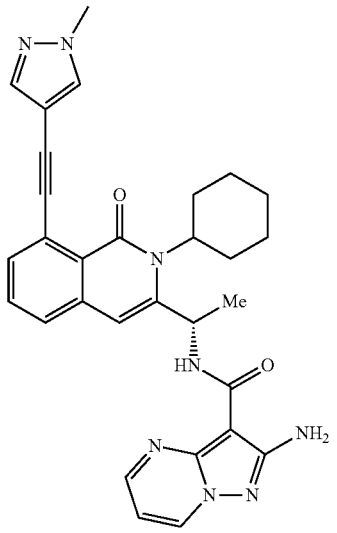
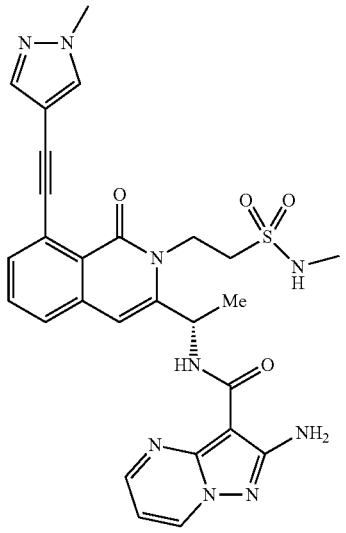
A suspension of aryl chloride (0.03-0.06 mmol), cesium carbonate (1.2 eq.), dichlorobis(acetonitrile)palladium (II) (0.05 eq.) and Xphos (0.15 eq.) in acetonitrile (2 mL) was bubbled with argon for 5 minutes. The mixture was charged with 4-ethynyl-1-methyl-1H-pyrazole (2 eq.), heated to 75° C. and stirred for 6 hr. The resulting mixture was cooled to RT, partitioned between ethyl acetate and water. The organic phase was separated, washed with saturated aqueous sodium chloride solution, dried with sodium sulfate and concentrated. The residue was purified on semi-prep HPLC (C-18) using a gradient of ACN/Water/Formic acid (9.9/90/0.1% to 49.9/50/0.1%) to afford the desired compound (confirmed by LCMS).

Compound no	Structure	ESI-MS m/z $[M + H]^+$
93		547.2
94		467.2
95		543.2

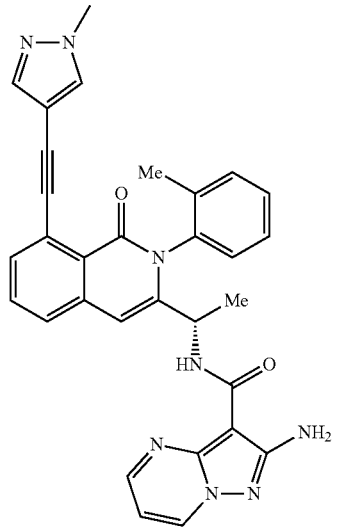
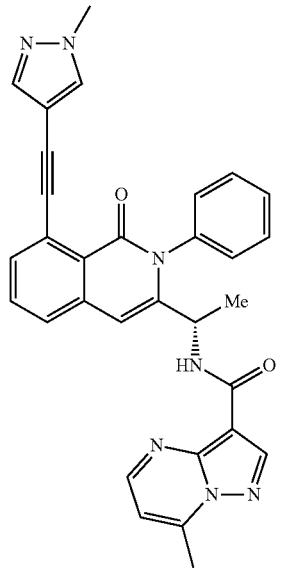
-continued

Compound no	Structure	ESI-MS m/z [M + H]+
96		547.2
97		565.2
98		543.2

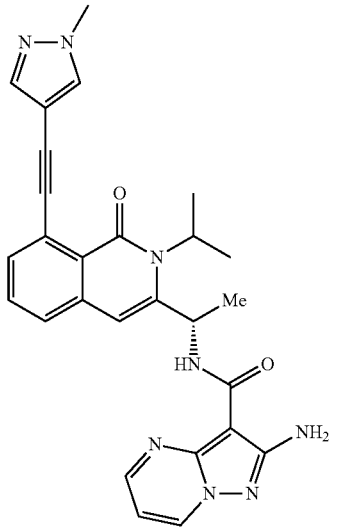
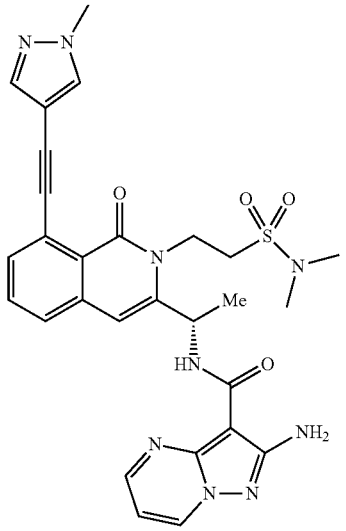
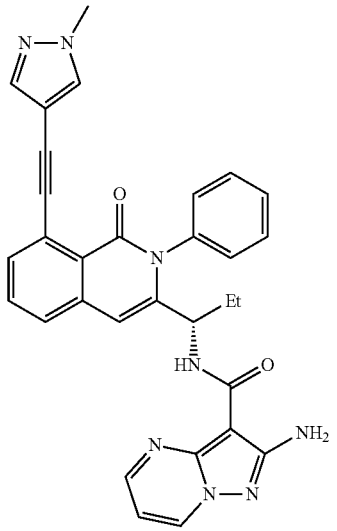
-continued

Compound no	Structure	ESI-MS m/z [M + H]+
99		535.3
100		574.2

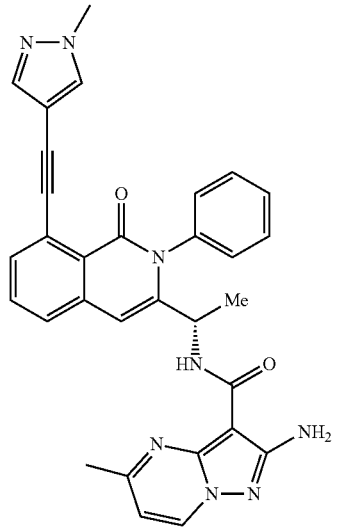
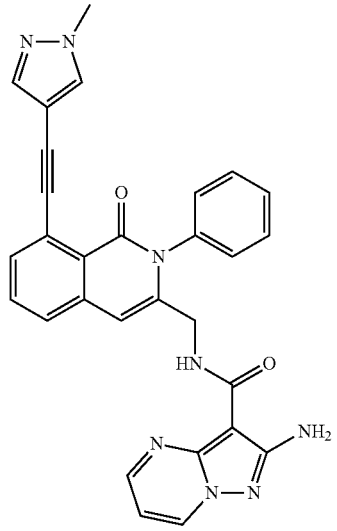
-continued

Compound no	Structure	ESI-MS m/z [M + H]+
101		543.2
102		543.2

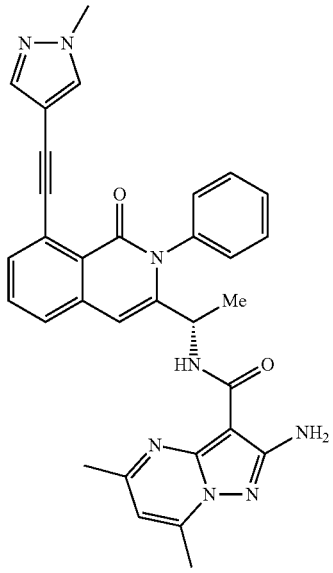
-continued

Compound no	Structure	ESI-MS m/z [M + H]+
103		495.2
104		588.2
105		543.3

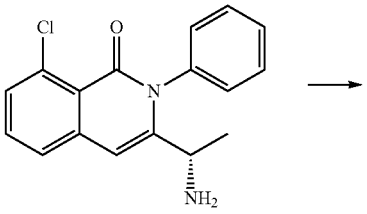
-continued

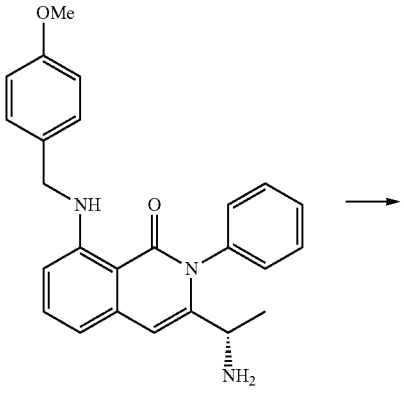
Compound no	Structure	ESI-MS m/z [M + H]+
106		543.3
107		515.2

-continued

Compound no	Structure	ESI-MS m/z [M + H]+
108		557.3

Example 42





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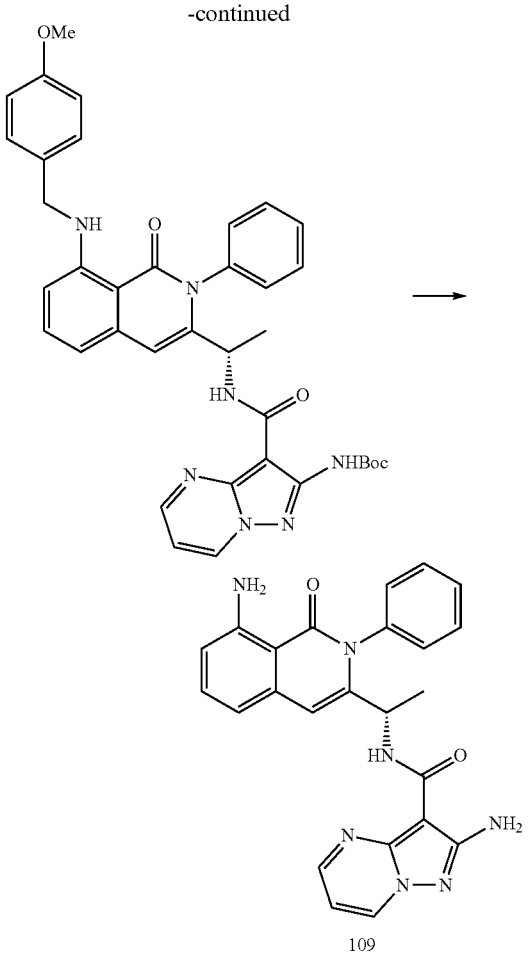


109

In a MW compatible vial, (S)-3-(1-aminoethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one (700 mg, 2.343 mmol), (4-methoxyphenyl)methanamine (3.2 g, 23.4 mmol, 20 eq.) and diisopropylethylamine (1.6 mL, 9.4 mmol, 4 eq.) were dissolved in NMP (12 mL). The vial was sealed and heated to 180° C. in a under MW irradiation and stirred for 6 hr. The reaction mixture was cooled to RT, partitioned between Ethyl acetate and water. The organic phase was separated, washed with saturated aqueous sodium chloride solution, dried with sodium sulfate and concentrated. The residue was purified with silica gel chromatography using a gradient of DCM and MeOH to afford (S)-3-(1-aminoethyl)-8-((4-methoxybenzyl) amino)-2-phenylisoquinolin-1(2H)-one. ESI-MS m/z: 400.1 $[M+H]^+$. (S)-3-(1-aminoethyl)-8-((4-methoxybenzyl) amino)-2-phenylisoquinolin-1(2H)-one (720 mg, 1.8 mmol), 2-((tert-butoxycarbonyl)amino)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (1.2 g, 4.31 mmol, 2.4 eq.), HOBt (700 mg, 4.57 mmol, 2.5 eq.) and EDC (800 mg, 4.17 mmol, 2.3 eq.) were suspended in DMF (30 mL). The reaction mixture was charged with diisopropylethylamine (2 mL, 11.45 mmol, 6.4 eq.) and stirred at RT for 1 hr. The reaction mixture was partitioned between Ethyl acetate and water. The organic phase was separated, washed with saturated aqueous sodium chloride solution, dried with sodium sulfate and concentrated. The residue was purified with silica gel chromatography using a gradient of Ethyl acetate and hexanes and triturated with MeOH to afford (S)-tert-butyl (3-((1-(8-((4-methoxybenzyl)amino)-1-oxo-2-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl)carbamoyl)pyrazolo[1,5-a] pyrimidin-2-yl)carbamate. ESI-MS m/z: 660.3 $[M+H]^+$. (S)-tert-butyl (3-((1-(8-((4-methoxybenzyl)amino)-1-oxo-2-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl)carbamoyl) pyrazolo[1,5-a]pyrimidin-2-yl)carbamate (360 mg, 0.546 mmol) and anisole (238 μL, 2.183 mmol, 4 eq.) was dissolved TFA (2 mL) and stirred at 60° C. for 1 hr. The reaction mixture was poured in a saturated aqueous bicarbonate solution. The organic phase was dried with sodium sulfate and concentrated. The residue was purified with silica gel chromatography using a gradient of DCM. The residue was purified on semi-prep HPLC (C-18) using a gradient of ACN/Water/Formic acid to afford (S)-2-amino-N-(1-(8-amino-1-oxo-2-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl)pyrazolo[1,5-a] pyrimidine-3-carboxamide. ESI-MS m/z: 440.2 $[M+H]^+$.

Biological Activity Assessment

TABLE 2

In Vitro IC_{50} data for selected compounds.

Compound no.	PI3K α IC_{50}	PI3K β IC_{50}	PI3K δ IC_{50}	PI3K γ IC_{50}	RAJI p110 δ assay IC_{50}	Raw264.7 p110 γ assay IC_{50}	PI3K δ/ PI3K γ IC_{50} (selectivity)	RAJI δ/ Raw264.7 γ IC_{50} (selectivity)
1	D2	C2	B2	A3	A4	A5	X	X
2	D2	D2	D2	C3	C4	A5	X	Y
3	D2	D2	D2	D3	D4	B5	W	X
4	C2	C2	D2	A3	B4	A5	Y	Y
5	D2	D2	A2	D3	A4	A5	V	W
6	D2	D2	D2	B3	C4	A5	Y	X
7	D2	D2	D2	B3	C4	A5	Y	Y
8	D2	D2	D2	C3	D4	C5	X	W
9	C2	C2	C2	B3	B4	A5	X	Y
10	D2	D2	D2	B3	D4	A5	X	X
11	D2	D2	D2	B3	D4	B5	X	X
12	D2	C2	C2	A3	B4	A5	X	X
13	D2	C2	B2	A3	A4	A5	X	W
14	C2	C2	A2	A3	A4	A5	X	W
15	D2	D2	B2	A3	B4	A5	X	W
16	D2	C2	C2	A3	B4	A5	Y	X
17	D2	D2	D2	B3	B4	A5	Y	Y
18	D2	D2	D2	B3	B4	A5	Y	X
19	D2	D2	D2	B3	C4	A5	Y	Y
20	D2	D2	C2	A3	B4	A5	X	X
21	D2	D2	D2	A3	B4	A5	Y	Y

TABLE 2-continued

In Vitro IC_{50} data for selected compounds.

Compound no.	PI3K α IC_{50}	PI3K β IC_{50}	PI3K δ IC_{50}	PI3K γ IC_{50}	RAJI p110 δ assay IC_{50}	Raw264.7 p110 γ assay IC_{50}	PI3K δ/ PI3K γ IC_{50} (selectivity)	RAJI δ/ Raw264.7 γ IC_{50} (selectivity)
22	D2	D2	D2	B3	D4	A5	X	X
23	C2	C2	D2	D3	B4	A5	W	W
24	C2	C2	C2	D3	B4	A5	W	W
25	C2	C2	D2	C3	B4	A5	X	X
26	D2	D2	D2	B3	B4	A5	X	Y
27	D2	D2	D2	B3	A4	A5	X	Y
28	D2	D2	D2	D3	B4	A5	W	X
29	D2	C2	C2	B3	A4	A5	X	W
30	D2	D2	D2	B3	B4	A5	Y	Y
31	D2	D2	D2	B3	B4	B5	X	W
32	D2	D2	D2	B3	C4	A5	Y	Y
33	D2	D2	D2	A3	B4	A5	Y	W
34	D2	D2	D2	C3	C4	B5	X	X
35	D2	D2	D2	B3	C4	A5	Y	Y
36	C2	A2	C2	A3	B4	C5	X	W
37	D2	D2	D2	D3	D4	A5	W	Y
38	D2	D2	D2	A3	C4	A5	Y	Y
39	D2	D2	D2	B3	D4	B5	X	X
40	C2	D2	D2	A3	B4	A5	Y	Y
41	D2	D2	D2	B3	B4	A5	Y	Y
42	D2	D2	D2	B3	C4	A5	X	X
43	D2	D2	D2	B3	B4	A5	Y	X
44	D2	C2	C2	D3	A4	B5	W	V
45	D2	D2	D2	B3	B4	A5	Y	W
46	D2	C2	C2	A3	A4	A5	Y	W
47	C2	A2	A2	A3	ND	ND	V	ND
48	C2	B2	C2	C3	A4	A5	W	V
49	D2	C2	C2	A3	A4	A5	X	V
50	D2	D2	C2	A3	A4	A5	Y	W
51	D2	C2	C2	B3	A4	A5	W	W
52	D2	D2	D2	B3	C4	A5	Y	Y
53	D2	D2	D2	D3	C4	B5	W	X
54	C2	C2	C2	A3	B4	A5	Y	W
55	C2	C2	D2	D3	C4	A5	W	X
56	D2	D2	D2	B3	B4	C5	X	V
57	D2	D2	D2	C3	B4	B5	W	W
58	D2	D2	D2	D3	C4	C5	W	V
59	D2	D2	D2	B3	B4	A5	X	X
60	D2	D2	D2	B3	B4	A5	X	Y
61	D2	D2	D2	C3	D4	A5	X	Y
62	D2	D2	D2	C3	D4	C5	X	V
63	D2	D2	D2	A3	C4	A5	Y	Y
64	D2	D2	D2	D3	D4	C5	W	X
65	D2	D2	D2	D3	D4	C5	W	X
66	D2	C2	C2	A3	B4	A5	X	X
67	D2	D2	D2	D3	D4	C5	W	X
68	D2	D2	D2	D3	D4	C5	W	W
69	D2	D2	D2	D3	ND	C5	W	ND
70	D2	D2	D2	B3	A4	A5	X	X
71	D2	D2	D2	E3	D4	ND	V	ND
72	D2	D2	D2	C3	D4	C5	X	W
73	D2	D2	D2	B3	C4	A5	X	Y
74	D2	D2	C2	C3	D4	C5	W	W
75	D2	D2	D2	D3	D4	A5	W	Y
76	D2	D2	D2	B3	B4	A5	Y	X
77	D2	D2	D2	A3	C4	A5	Y	Y
78	D2	D2	D2	B3	B4	A5	X	X
79	D2	D2	D2	C3	D4	A5	X	Y
80	C2	C2	D2	A3	B4	A5	Y	Y
81	C2	C2	C2	A3	ND	ND	Y	ND
82	D2	D2	D2	B3	C4	A5	X	X
83	D2	D2	D2	C3	C4	A5	X	X
84	D2	D2	D2	A3	B4	A5	Y	X
85	D2	D2	D2	C3	ND	ND	X	ND
86	D2	C2	C2	B3	ND	ND	X	ND
87	D2	D2	D2	E3	ND	ND	V	ND
88	D2	D2	D2	B3	B4	A5	X	Y
89	D2	D2	D2	C3	D4	A5	X	Y
90	D2	D2	D2	D3	D4	C5	W	X
91	D2	D2	D2	C3	B4	C5	W	W
92	D2	D2	C2	C3	B4	C5	W	V
93	D2	D2	D2	A3	ND	ND	Y	ND
94	C2	B2	D2	B3	ND	ND	X	ND

TABLE 2-continued

In Vitro IC_{50} data for selected compounds.

Compound no.	PI3K α IC_{50}	PI3K β IC_{50}	PI3K δ IC_{50}	PI3K γ IC_{50}	RAJI p110 δ assay IC_{50}	Raw264.7 p110 γ assay IC_{50}	PI3K δ/ PI3K γ IC_{50} (selectivity)	RAJI δ/ Raw264.7 γ IC_{50} (selectivity)
95	D2	D2	D2	B3	ND	ND	X	ND
96	C2	D2	D2	A3	ND	ND	Y	ND
97	D2	D2	D2	B3	ND	ND	X	ND
98	D2	D2	D2	B3	ND	ND	X	ND
99	D2	D2	D2	D3	ND	ND	X	ND
100	C2	C2	D2	A3	ND	ND	Y	ND
101	D2	D2	D2	A3	ND	ND	Y	ND
102	D2	D2	D2	B3	ND	ND	X	ND
103	D2	D2	D2	C3	ND	ND	X	ND
104	C2	C2	D2	A3	ND	ND	Y	ND
105	C2	D2	D2	A3	ND	ND	Y	ND
106	D2	C2	D2	A3	ND	ND	Y	ND
107	D2	D2	D2	D3	ND	ND	X	ND
108	D2	D2	D2	B3	ND	ND	X	ND
109	D2	C2	C2	A3	ND	ND	X	ND

The data in Table 2 are coded as follows.

For PI3K α, β, and δ IC_{50}:	For P13K γ IC_{50}:	RAJI p110 δ assay IC_{50}	Raw264.7 p110 γ assay IC_{50}
A2 = 1 to <500 nM	A3 = 1 to <100 nM	A4 = 1 to <100 nM	A5 = 1 to <50 nM
B2 = 500 to <1000 nM	B3 = 100 to <500 nM	B4 = 100 to <500 nM	B5 = 50 to <100 nM
C2 = 1000 to <5000 nM	C3 = 500 to <1000 nM	C4 = 500 to <1000 nM	C5 = 100 to <10000 nM
D2 = 5000 to 10000 nM	D3 = 1000 to 5000 nM	D4 = 1000 to 10000 nM	
	E3 = >5000 nM		

δ/γ IC_{50} selectivity:
V = 0.1 to 1
W = >1 to <10
X = 10 to <50
Y = 50 to <850
ND = not determined

Example 222

PI3-Kinase HTRF™ Assay

A PI3-Kinase HTRF® assay kit (cat No. 33-016) purchased from Millipore Corporation was used to screen compounds provided herein. This assay used specific, high affinity binding of the GRP1 pleckstrin homology (PH) domain to PIP3, the product of a Class 1A or 1B PI3 Kinase acting on its physiological substrate PIP2. During the detection phase of the assay, a complex was generated between the GST-tagged PH domain and biotinylated short chain PIP3. The biotinylated PIP3 and the GST-tagged PH domain recruited fluorophores (Streptavidin-Allophycocyanin and Europium-labeled anti-GST respectively) to form the fluorescence resonance energy transfer (FRET) architecture, generating a stable time-resolved FRET signal. The FRET complex was disrupted in a competitive manner by non-biotinylated PIP3, a product formed in the PI3 Kinase assay.

PI3 Kinase α, β, γ or δ activity was assayed using the PI3 Kinase HTRF® assay kit (catalogue No. 33-016) purchased from Millipore Corporation. Purified recombinant PI3Kα (catalogue No. 14-602-K), PI3Kβ (catalogue No. 14-603-K), PI3Kγ (catalogue No. 14-558-K), and PI3Kδ (catalogue No. 14-604-K) were obtained from Millipore Corporation. Purified recombinant PI3K enzyme was used to catalyze the phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP2 at 10 μM) to phosphatidylinositol 3,4,5-trisphosphate (PIP3) in the presence of 10 μM ATP. The assay was carried out in 384-well format and detected using a Perkin Elmer EnVision Xcite Multilabel Reader. Emission ratios were converted into percent inhibitions and imported into GraphPad Prism software. The concentration necessary to achieve inhibition of enzyme activity by 50% (IC_{50}) was calculated using concentrations ranging from 20 μM to 0.1 nM (12-point curve). IC_{50} values were determined using a nonlinear regression model available in GraphPad Prism 5.

Example 223

Chemical Stability

The chemical stability of one or more subject compounds is determined according to standard procedures known in the art. The following details an exemplary procedure for ascertaining chemical stability of a subject compound. The default buffer used for the chemical stability assay is phosphate-buffered saline (PBS) at pH 7.4; other suitable buffers can be used. A subject compound is added from a 100 μM stock solution to an aliquot of PBS (in duplicate) to give a final assay volume of 400 μL, containing 5 μM test compound and 1% DMSO (for half-life determination a total sample volume of 700 μL is prepared). Reactions are incubated, with shaking, for 24 hours at 37° C.; for half-life determination samples are incubated for 0, 2, 4, 6, and 24 hours. Reactions are stopped by adding immediately 100 μL of the incubation mixture to 100 μL of acetonitrile and vortexing for 5 minutes. The samples are then stored at −20° C. until analysis by HPLC-MS/MS. Where desired, a control compound or a reference

compound such as chlorambucil (5 μM) is tested simultaneously with a subject compound of interest, as this compound is largely hydrolyzed over the course of 24 hours. Samples are analyzed via (RP)HPLC-MS/MS using selected reaction monitoring (SRM). The HPLC conditions consist of a binary LC pump with autosampler, a mixed-mode, C12, 2×20 mm column, and a gradient program. Peak areas corresponding to the analytes are recorded by HPLC-MS/MS. The ratio of the parent compound remaining after 24 hours relative to the amount remaining at time zero, expressed as percent, is reported as chemical stability. In case of half-life determination, the half-life is estimated from the slope of the initial linear range of the logarithmic curve of compound remaining (%) vs. time, assuming first order kinetics.

Example 224

Expression and Inhibition Assays of p110α/p85α, p110β/p85α, p110δ/p85α, and p110γ

Class I PI3-Ks can be either purchased (p110α/p85α, p110β/p85α, p110δ/p85α from Upstate, and p110γ from Sigma) or expressed as previously described (Knight et al., 2004). IC_{50} values are measured using either a standard TLC assay for lipid kinase activity (described below) or a high-throughput membrane capture assay. Kinase reactions are performed by preparing a reaction mixture containing kinase, inhibitor (2% DMSO final concentration), buffer (25 mM HEPES, pH 7.4, 10 mM $MgCl_2$), and freshly sonicated phosphatidylinositol (100 μg/ml). Reactions are initiated by the addition of ATP containing 10 μCi of γ-32P-ATP to a final concentration of 10 or 100 μM and allowed to proceed for 5 minutes at room temperature. For TLC analysis, reactions are then terminated by the addition of 105 μL 1N HCl followed by 160 μL $CHCl_3$:MeOH (1:1). The biphasic mixture is vortexed, briefly centrifuged, and the organic phase is transferred to a new tube using a gel loading pipette tip precoated with $CHCl_3$. This extract is spotted on TLC plates and developed for 3-4 hours in a 65:35 solution of n-propanol:1M acetic acid. The TLC plates are then dried, exposed to a phosphorimager screen (Storm, Amersham), and quantitated. For each compound, kinase activity is measured at 10-12 inhibitor concentrations representing two-fold dilutions from the highest concentration tested (typically, 200 μM). For compounds showing significant activity, IC_{50} determinations are repeated two to four times, and the reported value is the average of these independent measurements.

Other commercial kits or systems for assaying PI3-K activities are available. The commercially available kits or systems can be used to screen for inhibitors and/or agonists of PI3-Ks including, but not limited to, PI 3-Kinase α, β, δ, and γ. An exemplary system is PI 3-Kinase (human) HTRF™ Assay from Upstate. The assay can be carried out according to the procedures suggested by the manufacturer. Briefly, the assay is a time resolved FRET assay that indirectly measures PIP3 product formed by the activity of a PI3-K. The kinase reaction is performed in a microtiter plate (e.g., a 384 well microtiter plate). The total reaction volume is approximately 20 μL per well. In the first step, each well receives 2 μL of test compound in 20% dimethylsulphoxide resulting in a 2% DMSO final concentration. Next, approximately 14.5 μL of a kinase/PIP2 mixture (diluted in 1× reaction buffer) is added per well for a final concentration of 0.25-0.3 μg/mL kinase and 10 μM PIP2. The plate is sealed and incubated for 15 minutes at room temperature. To start the reaction, 3.5 μL of ATP (diluted in 1× reaction buffer) is added per well for a final concentration of 10 μM ATP. The plate is sealed and incubated for 1 hour at room temperature. The reaction is stopped by adding 5 μL of Stop Solution per well and then 5 μL of Detection Mix is added per well. The plate is sealed, incubated for 1 hour at room temperature, and then read on an appropriate plate reader. Data is analyzed and IC_{50}s are generated using GraphPad Prism 5.

Example 225

B Cell Activation and Proliferation Assay

The ability of one or more subject compounds to inhibit B cell activation and proliferation is determined according to standard procedures known in the art. For example, an in vitro cellular proliferation assay is established that measures the metabolic activity of live cells. The assay is performed in a 96 well microtiter plate using Alamar Blue reduction. Balb/c splenic B cells are purified over a Ficoll-Paque™ PLUS gradient followed by magnetic cell separation using a MACS B cell Isolation Kit (Miletenyi). Cells are plated in 90 μL at 50,000 cells/well in B Cell Media (RPMI+10% FBS+Penn/Strep+50 μM bME+5 mM HEPES). A compound provided herein is diluted in B Cell Media and added in a 10 μL volume. Plates are incubated for 30 min at 37° C. and 5% CO_2 (0.2% DMSO final concentration). A 50 μL B cell stimulation cocktail is then added containing either 10 μg/mL LPS or 5 μg/mL F(ab')2 Donkey anti-mouse IgM plus 2 ng/mL recombinant mouse IL4 in B Cell Media. Plates are incubated for 72 hours at 37° C. and 5% CO_2. A volume of 15 μL of Alamar Blue reagent is added to each well and plates are incubated for 5 hours at 37° C. and 5% CO_2. Alamar Blue fluoresce is read at 560Ex/590Em, and IC_{50} or EC_{50} values are calculated using GraphPad Prism 5.

Example 226

Tumor Cell Line Proliferation Assay

The ability of one or more subject compounds to inhibit tumor cell line proliferation can be determined according to standard procedures known in the art. For instance, an in vitro cellular proliferation assay can be performed to measure the metabolic activity of live cells. The assay is performed in a 96-well microtiter plate using Alamar Blue reduction. Human tumor cell lines are obtained from ATCC (e.g., MCF7, U-87 MG, MDA-MB-468, PC-3), grown to confluency in T75 flasks, trypsinized with 0.25% trypsin, washed one time with Tumor Cell Media (DMEM+10% FBS), and plated in 90 μL at 5,000 cells/well in Tumor Cell Media. A compound provided herein is diluted in Tumor Cell Media and added in a 10 μL volume. Plates are incubated for 72 hours at 37° C. and 5% CO_2. A volume of 10 μL of Alamar Blue reagent is added to each well and plates are incubated for 3 hours at 37° C. and 5% CO_2. Alamar Blue fluoresce is read at 560Ex/590Em, and IC_{50} values are calculated using GraphPad Prism 5.

Example 227

Antitumor Activity In Vivo

The compounds described herein can be evaluated in a panel of human and murine tumor models.

Paclitaxel-Refractory Tumor Models

1. Clinically-Derived Ovarian Carcinoma Model.

This tumor model is established from a tumor biopsy of an ovarian cancer patient. Tumor biopsy is taken from the

patient. The compounds described herein are administered to nude mice bearing staged tumors using an every 2 days×5 schedule.

2. A2780Tax Human Ovarian Carcinoma Xenograft (Mutated Tubulin).

A2780Tax is a paclitaxel-resistant human ovarian carcinoma model. It is derived from the sensitive parent A2780 line by co-incubation of cells with paclitaxel and verapamil, an MDR-reversal agent. Its resistance mechanism has been shown to be non-MDR related and is attributed to a mutation in the gene encoding the beta-tubulin protein. The compounds described herein can be administered to mice bearing staged tumors on an every 2 days×5 schedule.

3. HCT116/VM46 Human Colon Carcinoma Xenograft (Multi-Drug Resistant).

HCT116/VM46 is an MDR-resistant colon carcinoma developed from the sensitive HCT116 parent line. In vivo, grown in nude mice, HCT116/VM46 has consistently demonstrated high resistance to paclitaxel. The compounds described herein can be administered to mice bearing staged tumors on an every 2 days×5 schedule.

4. M5076 Murine Sarcoma Model

M5076 is a mouse fibrosarcoma that is inherently refractory to paclitaxel in vivo. The compounds described herein can be administered to mice bearing staged tumors on an every 2 days×5 schedule. One or more compounds as provided herein can be used in combination with other therapeutic agents in vivo in the multidrug resistant human colon carcinoma xenografts HCT/VM46 or any other model known in the art including those described herein.

In one aspect, compounds provided herein may be evaluated in the following models according to methods known in the art. The dosage and schedule of administration may be varied depending on the model. The results may be evaluated with those of selective delta inhibitors, and combinations of delta and gamma inhibitors, and/or with antibodies that block specific inhibitory receptors.

Pancreatic Models

KPC model is a transgenic mouse model of pancreatic ductal adenocarcinoma (PDA), in which there is conditional expression of both mutant KrasG12D and p53R172H alleles in pancreatic cells. Tumors develop spontaneously in this mouse over a period of 3-6 months, and can be used to study prophylactic, as well as therapeutic efficacy with novel agents. Cells from these KPC tumors can also be adoptively transferred into syngeneic B6.129 hybrid mice, creating a model with a shorter latency period and allowing large number of animals with tumors to be synchronously established. See e.g., Cancer Cell 7:468 (2005).

Pan02 model: The murine pancreatic adenocarcinoma cell line Pan02 is a nonmetastatic tumor line, syngeneic to C57BL/6. It can be studied following s.c. injection into flank, or orthotopically following injection directly into the pancreas. See e.g., Cancer Res. 44: 717-726 (1984).

Lung Models

LLC Lewis Lung Adenocarcinoma model: LLC cells are derived from a spontaneous lung tumor from a C57BL/6 mouse and can be studied as a s.c. tumor when injected in the flank, or as an orthotopic tumor if injected i.v., following which it localizes to the lung.

LLC cells have also been modified to express a peptide from ovalbumin (LL2-OVA cells). Use of these cells, following either s.c. or i.v. injection, allows the tracking of OVA-specific CD8+lymphocyctes and measurement of effects of therapy on the adaptive immune response against the tumor. See e.g., Science 330:827 (2010).

Breast Model

The 4T1 mammary carcinoma is a transplantable tumor cell line that grows in syngeneic BALB/c mice. It is highly tumorigenic and invasive and, unlike most tumor models, can spontaneously metastasize from the primary tumor in the mammary gland to multiple distant sites including lymph nodes, blood, liver, lung, brain, and bone. See e.g., Current Protocols in Immunology Unit 20.2 (2000).

Lymphoma Model

EL4 is a C57BL/6 T thymoma and EG7 is an OVA-expressing subclone of EL4. The parental EL4 line has been modified to constitutively express luciferase, which allows non-invasive imaging of tumor growth throughout the animal using the Xenogen imaging platform.

Melanoma Model

B16 murine melanoma cells are syngeneic with C57BL/6 mice and can be studied after s.c. or i.v. injection. Placement at either site will result in metastases to lung and other organs. This model has been extensively studied in terms of the role that inhibitory receptors play in the anti-tumor immune response. See e.g., PNAS 107:4275 (2010).

Example 228

Microsome Stability Assay

The stability of one or more subject compounds is determined according to standard procedures known in the art. For example, stability of one or more subject compounds is established by an in vitro assay. For example, an in vitro microsome stability assay is established that measures stability of one or more subject compounds when reacting with mouse, rat or human microsomes from liver. The microsome reaction with compounds is performed in 1.5 mL Eppendorf tube. Each tube contains 0.1 μL of 10.0 mg/mL NADPH; 75 μL of 20.0 mg/mL mouse, rat or human liver microsome; 0.4 μL of 0.2 M phosphate buffer, and 425 μL of ddH_2O. Negative control (without NADPH) tube contains 75 μL of 20.0 mg/mL mouse, rat or human liver microsome; 0.4 μL of 0.2 M phosphate buffer, and 525 μL of ddH_2O. The reaction is started by adding 1.0 μL of 10.0 mM tested compound. The reaction tubes are incubated at 37° C. 100 μL sample is collected into new Eppendorf tube containing 300 μL cold methanol at 0, 5, 10, 15, 30 and 60 minutes of reaction. Samples are centrifuged at 15,000 rpm to remove protein. Supernatant of centrifuged sample is transferred to new tube. Concentration of stable compound after reaction with microsome in the supernatant is measured by Liquid Chromatography/Mass Spectrometry (LC-MS).

Example 229

Plasma Stability Assay

The stability of one or more subject compounds in plasma is determined according to standard procedures known in the art. See, e.g., *Rapid Commun. Mass Spectrom.,* 10: 1019-1026. The following procedure is an HPLC-MS/MS assay using human plasma; other species including monkey, dog, rat, and mouse are also available. Frozen, heparinized human plasma is thawed in a cold water bath and spun for 10 minutes at 2000 rpm at 4° C. prior to use. A subject compound is added from a 400 μM stock solution to an aliquot of pre-warmed plasma to give a final assay volume of 400 μL (or 800 μL for half-life determination), containing 5 μM test compound and 0.5% DMSO. Reactions are incubated, with shaking, for 0 minutes and 60 minutes at 37 C, or for 0, 15, 30, 45 and 60

minutes at 37 C for half life determination. Reactions are stopped by transferring 50 μL of the incubation mixture to 200 μL of ice-cold acetonitrile and mixed by shaking for 5 minutes. The samples are centrifuged at 6000×g for 15 minutes at 4° C. and 120 μL of supernatant removed into clean tubes. The samples are then evaporated to dryness and submitted for analysis by HPLC-MS/MS.

In one embodiment, one or more control or reference compounds (5 μM) are tested simultaneously with the test compounds: one compound, propoxycaine, with low plasma stability and another compound, propantheline, with intermediate plasma stability.

Samples are reconstituted in acetonitrile/methanol/water (1/1/2, v/v/v) and analyzed via (RP)HPLC-MS/MS using selected reaction monitoring (SRM). The HPLC conditions consist of a binary LC pump with autosampler, a mixed-mode, C12, 2×20 mm column, and a gradient program. Peak areas corresponding to the analytes are recorded by HPLC-MS/MS. The ratio of the parent compound remaining after 60 minutes relative to the amount remaining at time zero, expressed as percent, is reported as plasma stability. In case of half-life determination, the half-life is estimated from the slope of the initial linear range of the logarithmic curve of compound remaining (%) vs. time, assuming first order kinetics.

Example 230

Kinase Signaling in Blood

PI3K/Akt/mTOR signaling is measured in blood cells using the phosflow method (*Methods Enzymol*. (2007) 434: 131-54). This method is by nature a single cell assay so that cellular heterogeneity can be detected rather than population averages. This allows concurrent distinction of signaling states in different populations defined by other markers. Phosflow is also highly quantitative. To test the effects of one or more compounds provided herein, unfractionated splenocytes, or peripheral blood mononuclear cells are stimulated with anti-CD3 to initiate T-cell receptor signaling. The cells are then fixed and stained for surface markers and intracellular phosphoproteins Inhibitors provided herein inhibit anti-CD3 mediated phosphorylation of Akt-S473 and S6, whereas rapamycin inhibits S6 phosphorylation and enhances Akt phosphorylation under the conditions tested.

Similarly, aliquots of whole blood are incubated for 15 minutes with vehicle (e.g., 0.1% DMSO) or kinase inhibitors at various concentrations, before addition of stimuli to crosslink the T cell receptor (TCR) (anti-CD3 with secondary antibody) or the B cell receptor (BCR) using anti-kappa light chain antibody (Fab'2 fragments). After approximately 5 and 15 minutes, samples are fixed (e.g., with cold 4% paraformaldehyde) and used for phosflow. Surface staining is used to distinguish T and B cells using antibodies directed to cell surface markers that are known to the art. The level of phosphorylation of kinase substrates such as Akt and S6 are then measured by incubating the fixed cells with labeled antibodies specific to the phosphorylated isoforms of these proteins. The population of cells are then analyzed by flow cytometry.

Example 231

Colony Formation Assay

Murine bone marrow cells freshly transformed with a p190 BCR-Abl retrovirus (herein referred to as p190 transduced cells) are plated in the presence of various drug combinations in M3630 methylcellulose media for about 7 days with recombinant human IL-7 in about 30% serum, and the number of colonies formed is counted by visual examination under a microscope.

Alternatively, human peripheral blood mononuclear cells are obtained from Philadelphia chromosome positive (Ph+) and negative (Ph−) patients upon initial diagnosis or relapse. Live cells are isolated and enriched for CD19+ CD34+ B cell progenitors. After overnight liquid culture, cells are plated in methocult GF+ H4435 (Stem Cell Technologies), supplemented with cytokines (IL-3, IL-6, IL-7, G-CSF, GM-CSF, CF, Flt3 ligand, and erythropoietin) and various concentrations of known chemotherapeutic agents in combination with compounds of the present disclosure. Colonies are counted by microscopy 12-14 days later. This method can be used to test for evidence of additive or synergistic activity.

Example 232

In Vivo Effect of Kinase Inhibitors on Leukemic Cells

Female recipient mice are lethally irradiated from a γ source in two doses about 4 hr apart, with approximately 5Gy each. About 1 hr after the second radiation dose, mice are injected i.v. with about 1×10^6 leukemic cells (e.g., Ph+ human or murine cells, or p190 transduced bone marrow cells). These cells are administered together with a radioprotective dose of about 5×10^6 normal bone marrow cells from 3-5 week old donor mice. Recipients are given antibiotics in the water and monitored daily. Mice who become sick after about 14 days are euthanized and lymphoid organs are harvested for analysis. Kinase inhibitor treatment begins about 10 days after leukemic cell injection and continues daily until the mice become sick or a maximum of approximately 35 days post-transplant. Inhibitors are given by oral lavage.

Peripheral blood cells are collected approximately on day 10 (pre-treatment) and upon euthanization (post treatment), contacted with labeled anti-hCD4 antibodies and counted by flow cytometry. This method can be used to demonstrate that the synergistic effect of one or more compounds provided herein in combination with known chemotherapeutic agents can reduce leukemic blood cell counts as compared to treatment with known chemotherapeutic agents (e.g., Gleevec) alone under the conditions tested.

Example 233

Treatment of Lupus Disease Model Mice

Mice lacking the inhibitory receptor FcγRIIb that opposes PI3K signaling in B cells develop lupus with high penetrance. FcγRIIb knockout mice (R2KO, Jackson Labs) are considered a valid model of the human disease as some lupus patients show decreased expression or function of FcγRIIb (S. Bolland and J. V. Ravtech 2000. *Immunity* 12:277-285).

The R2KO mice develop lupus-like disease with antinuclear antibodies, glomerulonephritis and proteinurea within about 4-6 months of age. For these experiments, the rapamycin analogue RAD001 (available from LC Laboratories) is used as a benchmark compound, and administered orally. This compound has been shown to ameliorate lupus symptoms in the B6.Slelz.Sle3z model (T. Wu et al. *J. Clin Invest*. 117:2186-2196).

The NZB/W F1 mice that spontaneously develop a systemic autoimmune disease is a model of lupus. The mice are treated starting at 20 weeks of age for a profilactic model and

at 23 weeks of age for a therapeutic model. Blood and urine samples are obtained throughout the testing period, and tested for antinuclear antibodies (in dilutions of serum) or protein concentration (in urine). Serum is also tested for anti-ssDNA and anti-dsDNA antibodies by ELISA. Glomerulonephritis is assessed in kidney sections stained with H&E at the end of the study, or survival can be an endpoint. For example, the proteozome inhibitor Bortezimib is effective at blocking disease in the NZB/W model in both the profilactic and therapeutic model with reductions in auto-antibody production, kidney damage, and improvements in survival (*Nature Medicine* 14, 748-755 (2008)).

Lupus disease model mice such as R2KO, BXSB or MLR/lpr are treated at about 2 months old, approximately for about two months. Mice are given doses of: vehicle, RAD001 at about 10 mg/kg, or compounds provided herein at approximately 1 mg/kg to about 500 mg/kg. Blood and urine samples are obtained throughout the testing period, and tested for antinuclear antibodies (in dilutions of serum) or protein concentration (in urine). Serum is also tested for anti-ssDNA and anti-dsDNA antibodies by ELISA. Animals are euthanized at day 60 and tissues harvested for measuring spleen weight and kidney disease. Glomerulonephritis is assessed in kidney sections stained with H&E. Other animals are studied for about two months after cessation of treatment, using the same endpoints.

This established art model can be employed to demonstrate that the kinase inhibitors provided herein can suppress or delay the onset of lupus symptoms in lupus disease model mice.

Example 234

Murine Bone Marrow Transplant Assay

Female recipient mice are lethally irradiated from a γ ray source. About 1 hr after the radiation dose, mice are injected with about 1×10^6 leukemic cells from early passage p190 transduced cultures (e.g., as described in *Cancer Genet Cytogenet.* 2005 August; 161(1):51-6). These cells are administered together with a radioprotective dose of approximately 5×10^6 normal bone marrow cells from 3-5 wk old donor mice. Recipients are given antibiotics in the water and monitored daily. Mice who become sick after about 14 days are euthanized and lymphoid organs harvested for flow cytometry and/or magnetic enrichment. Treatment begins on approximately day 10 and continues daily until mice become sick, or after a maximum of about 35 days post-transplant. Drugs are given by oral gavage (p.o.). In a pilot experiment, a dose of chemotherapeutic that is not curative but delays leukemia onset by about one week or less is identified; controls are vehicle-treated or treated with chemotherapeutic agent, previously shown to delay but not cure leukemogenesis in this model (e.g., imatinib at about 70 mg/kg twice daily). For the first phase, p190 cells that express eGFP are used, and post-mortem analysis is limited to enumeration of the percentage of leukemic cells in bone marrow, spleen and lymph node (LN) by flow cytometry. In the second phase, p190 cells that express a tailless form of human CD4 are used and the post-mortem analysis includes magnetic sorting of hCD4+ cells from spleen followed by immunoblot analysis of key signaling endpoints: p Akt-T308 and 5473; pS6 and p4EBP-1. As controls for immunoblot detection, sorted cells are incubated in the presence or absence of kinase inhibitors of the present disclosure inhibitors before lysis. Optionally, "phosflow" is used to detect p Akt-S473 and pS6-S235/236 in hCD4-gated cells without prior sorting. These signaling studies are particularly useful if, for example, drug-treated mice have not developed clinical leukemia at the 35 day time point. Kaplan-Meier plots of survival are generated and statistical analysis done according to methods known in the art. Results from p190 cells are analyzed separated as well as cumulatively.

Samples of peripheral blood (100-200 μL) are obtained weekly from all mice, starting on day 10 immediately prior to commencing treatment. Plasma is used for measuring drug concentrations, and cells are analyzed for leukemia markers (eGFP or hCD4) and signaling biomarkers as described herein.

This general assay known in the art can be used to demonstrate that effective therapeutic doses of the compounds provided herein can be used for inhibiting the proliferation of leukemic cells.

Example 235

Matrigel Plug Angiogenesis Assay

Matrigel containing test compounds are injected subcutaneously or intraocularly, where it solidifies to form a plug. The plug is recovered after 7-21 days in the animal and examined histologically to determine the extent to which blood vessels have entered it. Angiogenesis is measured by quantification of the vessels in histologic sections. Alternatively, fluorescence measurement of plasma volume is performed using fluorescein isothiocyanate (FITC)-labeled dextran 150. The results are expected to indicate one or more compounds provided herein that inhibit angiogenesis and are thus expected to be useful in treating ocular disorders related to aberrant angiogenesis and/or vascular permeability.

Example 236

Corneal Angiogenesis Assay

A pocket is made in the cornea, and a plug containing an angiogenesis inducing formulation (e.g., VEGF, FGF, or tumor cells), when introduced into this pocket, elicits the ingrowth of new vessels from the peripheral limbal vasculature. Slow-release materials such as ELVAX (ethylene vinyl copolymer) or Hydron are used to introduce angiogenesis inducing substances into the corneal pocket. Alternatively, a sponge material is used.

The effect of putative inhibitors on the locally induced (e.g., sponge implant) angiogenic reaction in the cornea (e.g., by FGF, VEGF, or tumor cells). The test compound is administered orally, systemically, or directly to the eye. Systemic administration is by bolus injection or, more effectively, by use of a sustained-release method such as implantation of osmotic pumps loaded with the test inhibitor. Administration to the eye is by any of the methods described herein including, but not limited to eye drops, topical administration of a cream, emulsion, or gel, intravitreal injection.

The vascular response is monitored by direct observation throughout the course of the experiment using a stereomicroscope in mice. Definitive visualization of the corneal vasculature is achieved by administration of fluorochrome-labeled high-molecular weight dextran. Quantification is performed by measuring the area of vessel penetration, the progress of vessels toward the angiogenic stimulus over time, or in the case of fluorescence, histogram analysis or pixel counts above a specific (background) threshold.

The results can indicate one or more compounds provided herein inhibit angiogenesis and thus can be useful in treating ocular disorders related to aberrant angiogenesis and/or vascular permeability.

Example 237

Microtiter-Plate Angiogenesis Assay

The assay plate is prepared by placing a collagen plug in the bottom of each well with 5-10 cell spheroids per collagen plug each spheroid containing 400-500 cells. Each collagen plug is covered with 1100 μL of storage medium per well and stored for future use (1-3 days at 37° C., 5% CO_2). The plate is sealed with sealing. Test compounds are dissolved in 200 μL assay medium with at least one well including a VEGF positive control and at least one well without VEGF or test compound as a negative control. The assay plate is removed from the incubator and storage medium is carefully pipeted away. Assay medium containing the test compounds are pipeted onto the collagen plug. The plug is placed in a humidified incubator for (37° C., 5% CO_2) 24-48 hours. Angiogenesis is quantified by counting the number of sprouts, measuring average sprout length, or determining cumulative sprout length. The assay can be preserved for later analysis by removing the assay medium, adding 1 mL of 10% paraformaldehyde in Hanks BSS per well, and storing at 4° C. The results are expected to identify compounds that inhibit angiogenesis in various cell types tested, including cells of ocular origin.

Example 238

Combination Use of PI3K-δ Inhibitors and Agents that Inhibit IgE Production or Activity

The compounds as provided herein can present synergistic or additive efficacy when administered in combination with agents that inhibit IgE production or activity. Agents that inhibit IgE production include, for example, one or more of TEI-9874, 2-(4-(6-cyclohexyloxy-2-naphtyloxy)phenylacetamide)benzoic acid, rapamycin, rapamycin analogs (i.e., rapalogs), TORC1 inhibitors, TORC2 inhibitors, and any other compounds that inhibit mTORC1 and mTORC2. Agents that inhibit IgE activity include, for example, anti-IgE antibodies such as Omalizumab and TNX-901.

One or more of the subject compounds capable of inhibiting PI3K-δ can be efficacious in treatment of autoimmune and inflammatory disorders (AIID), for example, rheumatoid arthritis. If any of the compounds causes an undesired level of IgE production, one can choose to administer it in combination with an agent that inhibits IgE production or IgE activity. Additionally, the administration of PI3K-δ or PI3K-δ/γ inhibitors as provided herein in combination with inhibitors of mTOR can also exhibit synergy through enhanced inhibition of the PI3K pathway. Various in vivo and in vitro models can be used to establish the effect of such combination treatment on AIID including, but not limited to: (a) in vitro B-cell antibody production assay, (b) in vivo TNP assay, and (c) rodent collagen induced arthritis model.

(a) B-Cell Assay

Mice are euthanized, and the spleens are removed and dispersed through a nylon mesh to generate a single-cell suspension. The splenocytes are washed (following removal of erythrocytes by osmotic shock) and incubated with anti-CD43 and anti-Mac-1 antibody-conjugated microbeads (Miltenyi Biotec). The bead-bound cells are separated from unbound cells using a magnetic cell sorter. The magnetized column retains the unwanted cells and the resting B cells are collected in the flow-through. Purified B-cells are stimulated with lipopolysaccharide or an anti-CD40 antibody and interleukin 4 Stimulated B-cells are treated with vehicle alone or with PI3K-δ inhibitors as provided herein with and without mTOR inhibitors such as rapamycin, rapalogs, or mTORC1/C2 inhibitors. The results are expected to show that in the presence of mTOR inhibitors (e.g., rapamycin) alone, there is little to no substantial effect on IgG and IgE response. However, in the presence of PI3K-δ and mTOR inhibitors, the B-cells are expected to exhibit a decreased IgG response as compared to the B-cells treated with vehicle alone, and the B-cells are expected to exhibit a decreased IgE response as compared to the response from B-cells treated with PI3K-δ inhibitors alone.

(b) TNP Assay

Mice are immunized with TNP-Ficoll or TNP-KHL and treated with: vehicle, a PI3K-δ inhibitor, an mTOR inhibitor, for example rapamycin, or a PI3K-δ inhibitor in combination with an mTOR inhibitor such as rapamycin. Antigen-specific serum IgE is measured by ELISA using TNP-BSA coated plates and isotype specific labeled antibodies. It is expected that mice treated with an mTOR inhibitor alone exhibit little or no substantial effect on antigen specific IgG3 response and no statistically significant elevation in IgE response as compared to the vehicle control. It is also expected that mice treated with both PI3K-δ inhibitor and mTOR inhibitor exhibit a reduction in antigen specific IgG3 response as compared to the mice treated with vehicle alone. Additionally, the mice treated with both PI3K-δ inhibitor and mTOR inhibitor exhibit a decrease in IgE response as compared to the mice treated with PI3K-δ inhibitor alone.

(c) Rat Collagen Induced Arthritis Model

Female Lewis rats are anesthetized and given collagen injections prepared and administered as described previously on day 0. On day 6, animals are anesthetized and given a second collagen injection. Caliper measurements of normal (pre-disease) right and left ankle joints are performed on day 9. On days 10-11, arthritis typically occurs and rats are randomized into treatment groups. Randomization is performed after ankle joint swelling is obviously established and there is good evidence of bilateral disease.

After an animal is selected for enrollment in the study, treatment is initiated. Animals are given vehicle, PI3K-δ inhibitor, or PI3K-δ inhibitor in combination with rapamycin. Dosing is administered on days 1-6. Rats are weighed on days 1-7 following establishment of arthritis and caliper measurements of ankles taken every day. Final body weights are taken on day 7 and animals are euthanized.

The combination treatment using a compound as provided herein and rapamycin can provide greater efficacy than treatment with PI3K-δ inhibitor alone.

Example 239

Delayed Type Hypersensitivity Model

DTH is induced by sensitizing 60 BALB/c male mice on day 0 and day 1 with a solution of 0.05% 2,4 dinitrofluorobenzene (DNFB) in a 4:1 acetone/olive oil mixture. Mice are gently restrained while 20 μL of solution is applied to the hind foot pads of each mouse. The hind foot pads of the mice are used as they represent an anatomical site that can be easily isolated and immobilized without anesthesia. On day 5, mice are administered a single dose of vehicle, a compound provided herein at 10, 3, 1, or 0.3 mg/kg, or dexamethasone at a

dose of 5 mg/kg by oral gavage. Thirty minutes later mice are anaesthetized, and a solution of 0.25% DNFB in a 4:1 acetone/olive oil solution is applied to the left inner and outer ear surface. This application results in the induction of swelling to the left ear and under these conditions, all animals responded to this treatment with ear swelling. A vehicle control solution of 4:1 acetone/olive oil is applied to the right inner and outer ear. Twenty four hours later, mice are anaesthetized, and measurements of the left and right ear are taken using a digital micrometer. The difference between the two ears is recorded as the amount of swelling induced by the challenge of DNFB. Drug treatment groups are compared to vehicle control to generate the percent reduction in ear swelling. Dexamethasone is routinely used as a positive control as it has broad anti-inflammatory activity.

Example 240

Peptidoglycan-Polysaccharide Rat Arthritic Model

(a) Systemic Arthritis Model

All injections are performed under anesthesia. 60 female Lewis rats (150-170) are anesthetized by inhalation isoflurane using a small animal anesthesia machine. The animals are placed in the induction chamber until anesthetized by delivery of 4-5% isoflurane in O_2 and then held in that state using a nose cone on the procedure table. Maintenance level of isoflurane is at 1-2%. Animals are injected intraperitoneally (i.p.) with a single injection of purified PG-PS 10S Group A, D58 strain (concentration 25 μg/g of bodyweight) suspended in sterile 0.85% saline. Each animal receives a total volume of 500 microliters administered in the lower left quadrant of the abdomen using a 1 milliliter syringe with a 23 gauge needle. Placement of the needle is critical to avoid injecting the PG-PS 10S into either the stomach or caecum. Animals are under continuous observation until fully recovered from anesthesia and moving about the cage. An acute response of a sharp increase in ankle measurement, typically 20% above baseline measurement can peak in 3-5 days post injection. Treatment with test compounds can be PO, SC, IV or IP. Rats are dosed no more than two times in a 24 hour time span. Treatment can begin on day 0 or any day after that through day 30. The animals are weighed on days 0, 1, 2, 3, 4, 5, 6, 7 and beginning again on day 12-30 or until the study is terminated. Paw/ankle diameter is measured with a digital caliper on the left and right side on day 0 prior to injection and again on day 1, 2, 3, 4, 5, 6 and 7. On day 12, measurements begin again and continue on through day 30. At this time, animals can be anesthetized with isoflurane, as described above, and terminal blood samples can be obtained by tail vein draws for the evaluation of the compound blood levels, clinical chemistry or hematology parameters. Animals are then euthanized with carbon dioxide overdose. A thoracotomy can be conducted as a means of death verification.

(b) Monoarticular Arthritis Model

All injections are performed under anesthesia. 60 female Lewis rats (150-170) are anesthetized by inhalation isoflurane using a small animal anesthesia machine. The animals are placed in the induction chamber until anesthetized by delivery of 4-5% isoflurane in O_2 and then held in that state using a nose cone on the procedure table. Maintenance level of isoflurane is at 1-2%. Animals are injected intra-articular (i.a.) with a single injection of purified PG-PS 100P Group A, D58 strain (concentration 500 μg/mL) suspended in sterile 0.85% saline. Each rat receives a total volume of 10 microliters administered into the tibiotalar joint space using a 1 milliliter syringe with a 27 gauge needle. Animals are under continuous observation until fully recovered from anesthesia and moving about the cage. Animals that respond 2-3 days later with a sharp increase in ankle measurement, typically 20% above baseline measurement on the initial i.a. injection, are included in the study. On day 14, all responders are anesthetized again using the procedure previously described. Animals receive an intravenous (I.V.) injection of PG-PS (concentration 250 μL/mL). Each rat receives a total volume of 400 microliters administered slowly into the lateral tail vein using a 1 milliliter syringe with a 27 gauge needle. Baseline ankle measurements are measured prior to W injection and continue through the course of inflammation or out to day 10. Treatment with test compounds will be PO, SC, IV or IP. Rats are dosed no more than two times in a 24 hour time span. Treatment can begin on day 0 or any day after that through day 24. The animals are weighed on days 0, 1, 2, 3, 4, 5, and beginning again on day 14-24 or until the study is terminated. Paw/ankle diameter is measured with a digital caliper on the left and right side on day 0 prior to injection and again on day 1, 2, 3, 4, 5, and beginning again on day 14-24 or until the study is terminated. At this time, animals can be anesthetized with isoflurane, as described above, and terminal blood samples can be obtained by tail vein draws for the evaluation of the compound blood levels, clinical chemistry or hematology parameters. Animals are them euthanized with carbon dioxide overdose. A thoracotomy can be conducted as a means of death verification.

Example 241

Mice Models for Asthma

Efficacy of a compound provided herein in treating, preventing and/or managing asthma can be assessed using an conventional animal models including various mice models described in, for example, Nials et al., *Dis Model Mech.* 1(4-5): 213-220 (2008).

(a) Acute Allergen Challenge Models

Several models are known in the art and any of such models can be used. Although various allergens can be used to induce asthma-like conditions, the principle is consistent throughout the methods. Briefly, asthma-like conditions are induced through multiple systemic administration of the allergen (e.g., ova, house dust mite extracts and cockroach extracts) in the presence of an adjuvant such as aluminum hydroxide. Alternatively, an adjuvant-free system can be used, but it usually requires a higher number of exposures to achieve suitable sensitization. Once induced, animals exhibit many key features of clinical asthma such as: elevated levels of IgE; airway inflammation; goblet cell hyperplasia; epithelial hypertrophy; AHR ro specific stimuli; and early and late phase bronchoconstriction. Potential efficacy of a compound thus can be assessed by determining whether one or more of these clinical features are reversed or mitigated.

(b) Chronic Allergen Challenge Models

Chronic allergen challenge models aim to reproduce more of the features of the clinical asthma, such as airway remodeling and persistent AHR, than acute challenge models. While allergens similar to those used in acute allergen challenge models can be used, in chronic allergen challenge models, animals are subjected to repeated exposure of the airways to low levels of allergen for a period of up to 12 weeks. Once induced, animals exhibit key features of human asthma such as: allergen-dependent sensitization; a Th2-dependent allergic inflammation characterized by eosinophillic influx into the airway mucosa; AHR; and airway remodeling as evidenced by goblet cell hyperplasia, epithelial hypertrophy,

subepithelial or peribronchiolar fibrosis. Potential efficacy of a compound thus can be assessed by determining whether one or more of these clinical features are reversed or mitigated.

Example 242

Models for Psoriasis

Efficacy of a compound provided herein in treating, preventing and/or managing psoriasis can be assessed using an conventional animal models including various animal models described in, for example, Boehncke et al., *Clinics in Dermatology,* 25: 596-605 (2007).

As an example, the mouse model based on adoptive transfer of $CD4^+CD45RB^{hi}$ T cells described in Hong et al., *J. Immunol.,* 162: 7480-7491 (1999) can be made. Briefly, female BALB/cBY (donor) and C.B.-17/Prkdc scid/scid (recipient) mice are housed in a specific pathogen-free environment and are used between 6 and 8 weeks of age. $CD4^+$ T cells are enriched from BALB/cBy splenocytes using a mouse CD4 enrichment kit. The cells are then labeled with PE-conjugated anti-CD4, FITC-conjugated anti-CD45RB, and APC-conjugated anti-CD25 antibodies. Cells are sorted using a cell sorter. $CD4^+CD45RB^{hi}CD25$ cells are collected. Cells are resuspended in saline and 4×10^8 cells/mouse are injected i.p. into C.B.-17/Prkdc scid/scid mice. Mice may be dosed with LPS, cytokines, or antibodies as necessary. Mice are monitored for external signs of skin lesions twice each week. After the termination, ear, back skin, lymph nodes and spleen may be collected for further ex vivo studies.

Example 243

Models for Scleroderma

A compound's efficacy in treating scleroderma can be tested using animal models. An exemplary animal model is a mouse model for scleroderma induced by repeated local injections of bleomycin ("BLM") described, for example, in Yamamoto et al., *J Invest Dermatol* 112: 456-462 (1999), the entirety of which is incorporated herein by reference. This mouse model provides dermal sclerosis that closely resembles systemic sclerosis both histologically and biochemically. The sclerotic changes observed in the model include, but are not limited to: thickened and homogenous collagen bundles and cellular filtrates; gradual increase in number of mast cells; degranulation of mast cells; elevated histamine release; increase in hydroxyproline in skin; presence of anti-nuclear antibody in serum; and strong expression of transforming growth factor β-2 mRNA. Therefore, efficacy of a compound in treating scleroderma can be assessed by monitoring the lessening of one or more of these changes.

Briefly, the following exemplary procedures can be used to generate the mouse model for scleroderma: Specific pathogen-free, female BALB/C mice and C3H mice of 6 weeks old, weighing about 20 g, are purchased and maintained with food and water ad libitum. BLM is dissolved in PBS at differing concentrations and sterilized with filtration. Aliquots of each concentration of BLM or PBS are injected subcutaneously into the shaved back of the mice daily for 1-4 weeks with a needle. Alternatively, mice are injected every other day.

Histolopathological and biochemical changes induced can be assessed using any methods commonly practiced in the field. For example, histopathological changes can be assessed using a standard avidine-biotin peroxidase technique with anti-L3T4 monoclonal antibody, anti-Lyt2 monoclonal antibody, anti-mouse pan-tissue-fixed macrophage antibody, anti-stem cell factor monoclonal antibody, anti-transforming growth factor-β polyclonal antibody, and anti-decorin antibody. Cytokine expression of cellular infiltrates can be assessed by using several anti-cytokine antibodies. Hydroxyproline level can be assessed by hydrolyzing skin pieces with hydrochloric acid, neutralizing with sodium hydroxide, and colorimetric ally assessing the hydrolates at 560 nm with p-dimethylaminobenzaldehyde. Pepsin-resistant collagen can be assessed by treating collagen sample extracted from biopsied tissues and analyzing by polyacrylamide stacking gel electrophoresis. Mast cells can be identified by toluidine blue, and cells containing matachromatic granules can be counted under high magnification of a light microscope. Serum levels of various cytokines can be assessed by enzyme-linked immunosorbent assay, and mRNA levels of the cytokines can be assessed by reverse-transcriptase polymerase chain reaction. Autoantibodies in serum can be detected using 3T3 fibroblasts as the substrate for the screening.

Example 244

Models for Myositis

A compound's efficacy in treating myositis (e.g., dermatomyositis) can be tested using animal models known in the art. One such example is the familial canine dermatomyositis model described in Hargis et al., *AJP* 120(2): 323-325 (1985). Another example is the rabbit myosin induced mouse model described in Phyanagi et al., *Arthritis & Rheumatism,* 60(10): 3118-3127 (2009).

Briefly, 5-week old male SJL/J mice are used. Purified myosin from rabbit skeletal muscle (6.6 mg/ml) is emulsified with an equal amount of Freund's complete adjuvant and 3.3 mg/ml *Mycobacterium butyricum*. The mice are immunized repeatedly with emulsified rabbit myosin. Once myositis is induced, inflammatory cell filtration and necrotic muscle fiber should be evident in the model. In the muscles of animals, CD4 T cells are mainly located in the perimysum and $CD8^+$ T cells are mainly located in the endomysium and surround non-necrotic muscle fibers. TNFα, IFNγ and perforin are up-regulated and intercellular adhesion molecule 1 is increased in the muscles.

To assess the efficacy of a compound, following administration of the compound through adequate route at specified dose, the mice are killed and muscle tissues are harvested. The muscle tissue is immediately frozen in chilled isopentane precooled in liquid nitrogen, and then cryostat sections are prepared. The sections are stained with hematoxylin and eosin for counting of number of infiltrated cells. Three sections from each mouse are prepared and photomicrographs are obtained. For immunohistochemical tests, cryostat sections of muscle are dried and fixed in cold acetone at −20° C. The slides are rehydrated in PBS, and then endogeneous peroxide activity is blocked by incubation in 1% hydrogen peroxide. The sections are incubated overnight with rat anti-mouse CD4 monoclonal antibody, rat anti-mouse CD8 monoclonal antibody, rat anti-mouse F4/80 monoclonal antibody or normal rat IgG in antibody diluent. The samples are washed with PBS and incubated with biotin-conjugated rabbit anti-rat IgG pretreated with 5% normal mouse serum. After washing with PBS, the samples are incubated with streptavidin-horseradish peroxidase. After washing PBS, diaminobenzidine is used for visualization.

Example 245

Models for Sjögren Syndrome

A compound's efficacy in treating Sjögren's syndrome can be tested using animal models known in the art, for example,

those described in Chiorini et al., *Journal of Autoimmunity* 33: 190-196 (2009). Examples include: mouse model spontaneously developed in first filial generation of NZB mice crossed to NZW mice (see, e.g., Jonsson et al., *Clin Immunol Immunopathol* 42: 93-101 (1987); mouse model induced by i.p. injection of incomplete Freund's adjuvant (id.; Deshmukh et al., *J Oral Pathol Med* 38: 42-27 (2009)); NOD mouse models wherein Sjögren's phenotype is developed by specific genotypes (see, e.g., Cha et al., *Arthritis Rheum* 46: 1390-1398 (2002); Kong et al., *Clin Exp Rheumatol* 16: 675-681 (1998); Podolin et al., *J Exp Med* 178: 793-803 (1993); and Rasooly et al., *Clin Immunol Immunopathol* 81: 287-292 (1996)); mouse model developed in spontaneous lpr mutation; mouse model developed in Id3 knock-out mice (see, e.g., Li et al., *Immunity* 21: 551-560 (2004)); mouse model developed in PI3K knock-out mice (see, e.g., Oak et al., *Proc Natl Acad Sci USA* 103: 16882-16887 (2006)); mouse model developed in BAFF over-expressing transgenic mice (see, e.g., Groom et al., *J Clin Invest* 109: 59-68 (2002)); mouse model induced by injection of Ro antigen into BALB/c mice (see, e.g., Oh-Hora et al., *Nat. Immunol* 9: 432-443 (2008)); mouse model induced by injection of carbonic anhydrase II (see, e.g., Nishimori et al., *J Immunol* 154: 4865-4873 (1995); mouse model developed in IL-14 over-expressing transgenic mice (see, e.g., Shen et al., *J Immunol* 177: 5676-5686 (2006)); and mouse model developed in IL-12 expressing transgenic mice (see, e.g., McGrath-Morrow et al., *Am J Physiol Lung Cell Mol Physiol* 291: L837-846 (2006)).

Example 246

Models for Immune Complex Mediated Disease

The Arthus reaction is a type 3 immune response to immune complexes, and thus, can be a mechanistic model supporting therapeutic hypothesis for immune complex mediated diseases such as rheumatoid arthritis, lupus and other autoimmune diseases. For example, PI3Kγ and δ deficient mice can be used as experimental models of the Arthus reaction and provide assessment of therapeutic potential of a compound as to the treatment of immune complex mediated diseases. The Arthus reaction can be induced using the following exemplary procedures as described in Konrad et al., *Journal of Biological Chemistry* (2008 283(48): 33296-33303.

PI3Kγ- and PI3Kδ-deficient mice are maintained under dry barrier conditions. Mice are anesthetized with ketamine and xylazine, and the trachea is cannulated. Appropriate amount of protein G-purified anti-OVA IgG Ab is applied, and appropriate amount of OVA antigen is given intravenously. For PI3K blocking experiments, wortmanin is given intratracheally together with the application of anti-OVA igG. Mice are killed at 2-4 hours after initiation of inflammation, and desired follow up assessments can be performed using methods known in the art.

Example 247

PI3-Kinase Promega™ Assay

Promega ADP-Glo Max assay kit (Cat. No. V7002) was utilized to determine IC_{50} values for α, β, δ and γ isoforms of human Class I PI3 kinases (Millipore). Samples of kinase (20 nM α or δ, 40 nM β or γ isoform) were incubated with compound for 15 minutes at room temperature in reaction buffer (15 mM HEPES pH 7.4, 20 mM NaCl, 1 mM EGTA, 0.02% Tween 20, 10 mM $MgCl_2$, 0.2 mg/mL bovine-γ-globulins) followed by addition of ATP/diC8-PtdInsP mixture to give final concentrations of 3 mM ATP and 500 uM diC_8-PtdInsP. Reactions were incubated at room temperature for 2 hours followed by addition of 25 uL of stop solution. After a 40-minute incubation at room temperature, 50 uL of Promega detection mix was added followed by incubation for 1 hour at room temperature. Plates were then read on Envision plate reader in luminescence mode. Data was converted to % inhibition using the following equation below:

$$\%\ \text{inhibition} = 100 - \left(\left[\frac{S - Pos}{Neg - Pos}\right] * 100\right)$$

where S is the sample luminescence, Pos is a positive control without added PI3K, Neg is the negative control without added compound. Data was then plotted as % inhibition vs compound concentration. Data fit to 4 parameter logistic equation to determine IC_{50} values:

$$\%\ \text{Inhibition} = \frac{\max - \min}{1 - \left(\frac{IC_{50}{}^{h}}{[I]^{h}}\right)}$$

Certain compounds provided herein were tested in PI3-Kinase Promega Assay using procedures as described above to determine IC_{50} values for α, β, δ and/or γ isoforms. The IC_{50} values are summarized in Table 2.

Example 248

Isoform-Selective Cellular Assays

(a) PI3K-δ Selective Assay

A compound's ability in selectively inhibiting PI3K-δ can be assessed using RAJI cells, i.e., B lymphocyte cells derived from lymphoma patients. Briefly, serum-starved RAJI cells are stimulated with anti-human IgM, thereby causing signaling through the B-cell receptors, as described in, for example, He et al., *Leukemia Research* (2009) 33: 798-802. B-cell receptor signaling is important for the activation, differentiation, and survival of B cells and certain B-cell derived cancers. Reduction of phospho-AKT is indicative of compounds that may inhibit B-cell proliferation and function in certain diseases. By monitoring the reduction of phospho-AKT in stimulated RAJI cells (using for example, phospho-AKT antibodies), a compound's potential efficacy in selectively inhibiting PI3Kδ can be assessed.

Certain compounds provided herein were tested in RAJI cell model using procedures as described above. The IC_{50} values for phospho-AKT are summarized in Table 2.

(b) PI3K-γ Selective Assay

A compound's ability in selectively inhibiting PI3K-γ can be assessed using RAW264.7 macrophages. Briefly, serum-starved RAW264.7 cells are stimulated with a known GPCR agonist C5a. See, e.g., Camps et al., *Nature Medicine* (2005) 11(9):936-943. Cells can be treated with test compounds prior to, simultaneously with, or subsequent to the stimulation by C5a. RAW 264.7 cells respond to the complement component fragment C5a through activation of the C5a receptor, and the C5a receptor activates macrophages and induces cell migration. Test compounds' ability to inhibit C5a-mediated AKT phosphorylation is indicative of selective inhibition of PI3K-γ. Thus, by monitoring the reduction of phospho-AKT in stimulated RAW 264.7 cells (using for

example, phospho-AKT antibodies), a compound's potential efficacy in selectively inhibiting PI3Kγ can be assessed.

Certain compounds provided herein were tested in RAW 264.7 cell model using procedures as described above. The IC_{50} values for phospho-AKT are summarized in Table 2.

(c) PI3K-α Selective Assay

A compound's ability in selectively inhibiting PI3K-α can be assessed using SKOV-3 cells, i.e., human ovarian carcinoma cell line. Briefly, SKOV-3 cells, in which mutant PI3Kα is constitutively active, can be treated with test compounds. Test compounds' ability to inhibit AKT phosphorylation in SKOV-3 cells, therefore, is indicative of selective inhibition of PI3Kα. Thus, by monitoring the reduction of phospho-AKT in SKOV-3 cells (using for example, phospho-AKT antibodies), a compound's potential efficacy in selectively inhibiting PI3Kα can be assessed.

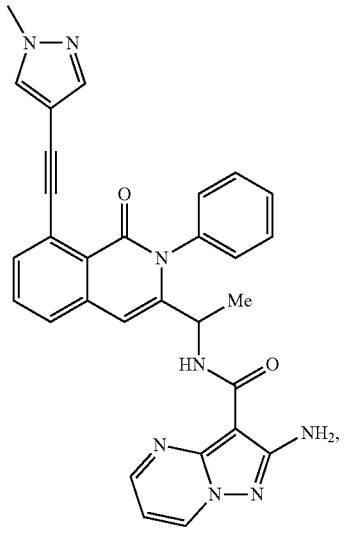
(d) PI3K-β Selective Assay

A compound's ability in selectively inhibiting PI3K-β can be assessed using 786-O cells, i.e., human kidney carcinoma cell line. Briefly, 786-O cells, in which PI3Kβ is constitutively active, can be treated with test compounds. Test compounds' ability to inhibit AKT phosphorylation in 786-O cells, therefore, is indicative of selective inhibition of PI3Kβ. Thus, by monitoring the reduction of phospho-AKT in 786-O cells (using for example, phospho-AKT antibodies), a compound's potential efficacy in selectively inhibiting PI3Kβ can be assessed.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims. Various publications, patents and patent applications are cited herein, the disclosures of which are incorporated by reference in their entireties.

What is claimed is:

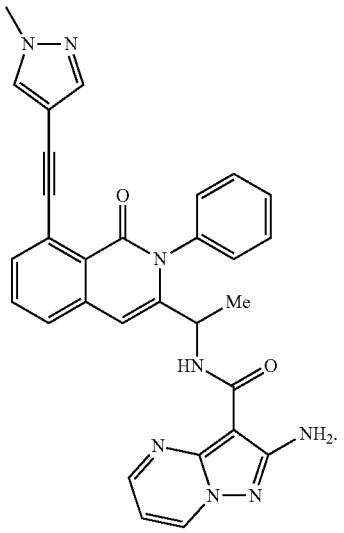
1. A compound of the formula:



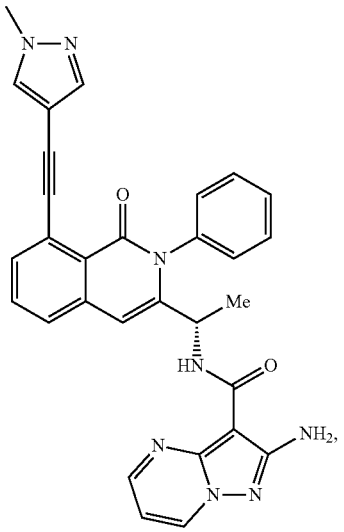
or a pharmaceutically acceptable form thereof, wherein the pharmaceutically acceptable form is a pharmaceutically acceptable salt, hydrate, solvate, enantiomer, or a mixture of enantiomers.

2. The compound of claim **1**, wherein the pharmaceutically acceptable form is a pharmaceutically acceptable salt, enantiomer, or a mixture of enantiomers.

3. A compound of the formula:



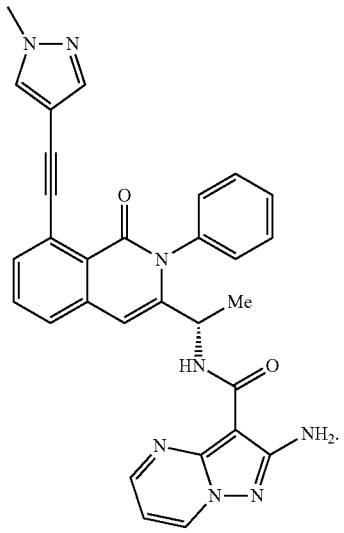
4. A compound of the formula:



or a pharmaceutically acceptable form thereof, wherein the pharmaceutically acceptable form is a pharmaceutically acceptable salt, hydrate, or solvate.

5. The compound of claim **4**, wherein the pharmaceutically acceptable form is a pharmaceutically acceptable salt.

6. A compound of the formula:



7. The compound of claim 2, wherein the compound has an (S)-enantiomeric excess of greater than 55%.

8. The compound of claim 2, wherein the compound has an (S)-enantiomeric excess of greater than 75%.

9. The compound of claim 2, wherein the compound has an (S)-enantiomeric excess of greater than 90%.

10. The compound of claim 2, wherein the compound has an (S)-enantiomeric excess of greater than 95%.

11. The compound of claim 2, wherein the compound has an (S)-enantiomeric excess of greater than 98%.

12. The compound of claim 2, wherein the compound has an (S)-enantiomeric excess of greater than 99%.

13. A pharmaceutical composition comprising a compound of claim 1 and one or more pharmaceutically acceptable excipients.

14. A pharmaceutical composition comprising a compound of claim 2 and one or more pharmaceutically acceptable excipients.

15. A pharmaceutical composition comprising a compound of claim 3 and one or more pharmaceutically acceptable excipients.

16. A pharmaceutical composition comprising a compound of claim 4 and one or more pharmaceutically acceptable excipients.

17. A pharmaceutical composition comprising a compound of claim 5 and one or more pharmaceutically acceptable excipients.

18. A pharmaceutical composition comprising a compound of claim 6 and one or more pharmaceutically acceptable excipients.

19. A pharmaceutical composition comprising a compound of claim 7 and one or more pharmaceutically acceptable excipients.

20. A pharmaceutical composition comprising a compound of claim 8 and one or more pharmaceutically acceptable excipients.

21. A pharmaceutical composition comprising a compound of claim 9 and one or more pharmaceutically acceptable excipients.

22. A pharmaceutical composition comprising a compound of claim 10 and one or more pharmaceutically acceptable excipients.

23. A pharmaceutical composition comprising a compound of claim 11 and one or more pharmaceutically acceptable excipients.

24. A pharmaceutical composition comprising a compound of claim 12 and one or more pharmaceutically acceptable excipients.

* * * * *